IVF IN THE NETHERLANDS

SUCCESS RATES, LIFESTYLE, PSYCHOLOGICAL FACTORS, AND COSTS

A.M.E. Lintsen

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Chapter | 1

General introduction

IVF in the Netherlands

In Vitro Fertilisation (IVF) is a technique to fertilise oocyte and spermatozoa, literally in glass, in a laboratory setting. IVF is applied in couples who have not conceived after a period of unprotected intercourse.
Since the beginning of IVF treatment in the Netherlands (1983), the number of treatments have gradually increased from around 1500 cycles per year in the first years (Haan *et al.,* 1991), to more than 11,000 cycles in 1996, and well over 16,000 cycles in 2007 (www.lirinfo.nl). The technique has also improved, which resulted in a higher chance of success per treatment. Initially the ongoing pregnancy rate (the chance of pregnancy, with ultrasound observed fetal heart beat, after at least 8 weeks gestation), was around 15 % per cycle (Haan *et al.,* 1991), and increased to an average of 25% per cycle in 2007. Today, one in every 39 newborns in the Netherlands originates from IVF or ICSI treatment (www.lirinfo.nl).

The increase in the number of treatments was due to a widening of indications for IVF treatment. Initially IVF was developed for women suffering from infertility because of bilateral tubal occlusion. Ten years after the introduction, also other female related subfertility causes such as: endometrioses, cervical hostility and hormonal disturbances were treated with IVF. Reduced semen quality of the partner, and unexplained subfertility became indications for IVF treatment as well. In 1992, with the development of Intra Cytoplasmic Sperm Injection (ICSI) (Palermo *et al.,* 1992), in which fertilisation takes place by injection of a single spermatozoon directly into the oocyt, the indications for assisted reproductive technology (ART) increased further. ICSI has become a treatment option for many couples with severe male subfertility, who would have no, or only a very low chance of fertilisation with IVF. The possibilities of treatments of in particular severe male infertility (ICSI) have expanded with surgical retrieved sperm, used in percutaneous epididymal sperm aspiration (PESA) and testicular sperm extraction (TESE).

Furthermore, the mean age at which Dutch women deliver their first child is 29,4 years, one of the highest worldwide (Uitstel van ouderschap, www.RVZ.nl). The physiological process of biological aging of the ovary results in a decrease of quantity and quality of the oocyte reserve and a lower natural pregnancy chance (te Velde and Pearson, 2002). As a consequence of postponement of maternity more couple will need ART.

In the Netherlands, the number of IVF centres with a license for an IVF laboratory is restricted by the Ministry of Health to 13 (Gezondheidsraad, Herziening Planningsbesluit 1997). Soon after the introduction of IVF, the increasing demand for ART exceeded the supply. This was partly overcome by the introduction of *transport*- and *satellite* clinics: To limit traveling time and

inconvenience for the patients, the first part of the IVF treatment is offered in the local hospitals by their own gynaecologists. After retrieval at the transport-clinics, the oocytes are "transported" to an IVF centre for the laboratory procedure. Satellite-clinics, monitor the ovarian stimulation "at a distance" from the IVF centre. Next, the couple is referred to the centre at the moment of oocyte retrieval (Roest *et al.,* 1995). This way, the capacity of the IVF laboratories is used effective without overburdening the medical staff of the IVF centre. Concentration of experience and expertise, another condition of the ministry, could also be guaranteed.

In the past 25 years all IVF centres and their laboratories have scaled up. The 13 IVF centres start between 300-2000 treatment cycles a year (mean number of treatments per IVF centre in 2006 was 1105). The average ongoing pregnancy chance per cycle of IVF or ICSI treatment is 25%, but may vary from year to year explained by the differences in population treated (patient mix) and by pure chance (www.lirinfo.nl).
In the early years of IVF in the Netherlands, differences in pregnancy rate between 5 IVF centres were found, even after adjustment for patient mix (Haan *et al.,* 1991). It is interesting to know if this still holds true today.

Patient characteristics

Reproduction is a matter of chance. The monthly probability is more or less constant, but between couples there is a wide variability in chance *(*te Velde *et al.,* 2000*).* Dependent on different patient characteristics the chance of pregnancy could be predictable.
With increasing women's age the pregnancy chance diminishes. Female fertility is limited by a biological age-dependent process and studied in natural fertility populations (Eijkemans, thesis, 2004). The decline in fertility is expressed in a decreasing quantity and quality of the available oocytes and follicle pool.
Subfertility, defined as a failure to become pregnant after at least 12 months of unprotected intercourse, can be categorized by the cause. With diagnostic examination a distinction into female factors, e.g. tubal occlusion, hormonal disturbances, or a male related subfertility can be made. In around 30% of all subfertile couples the reason cannot be found.
For subfertile couples treated with IVF, the impact of female age on the chance of pregnancy was found to be the most important determinant of success. The degree of subfertility can be expressed in a period of time, or the duration a couple has been unsuccessful at conceiving. With a history of pregnancy (secondary subfertility), and in particular when IVF had led to a live birth, the chance of pregnancy was higher compared to women with a primary subfertility. The influence of the diagnostic category on the chance of pregnancy is less clear (Templeton *et al,.* 1996).

A combined influence of the different subfertility related patient characteristics on the pregnancy chance with and without treatment, would give a prognosis of pregnancy and could be used to decide whether to start treatment IVF or not (yet).
Lifestyle, such as overweight and smoking as possible confounders on the fertility of a couple are studied worldwide on a large scale. Although research on lifestyle factors cannot reach the highest levels of evidence for ethical reasons, large cohort studies on the negative impact of lifestyle factors on IVF treatment, may lead to more awareness of patients and professionals on this subject and maybe to a change of habits.
Besides patient characteristics and lifestyle, the influence of psychological factors on subfertility have been an issue of interest for several years. The "evidence" that stress has a negative impact on fertility is well known by laymen. Many of them know the examples of subfertile couples who finally succeed in having a spontaneous pregnancy after going on a holiday, moving to another house, and/or being occupied with something else than the fertility problem. The scientific evidence of the influence of distress as a determinant on fertility is however contradictory.

IVF guideline

So far, only for tubal pathology there is scientific evidence of the surplus probability over waiting for a spontaneous pregnancy (Soliman *et al.,* 1993). For couples with other reasons for subfertility, IVF is still not evidence based. Not only in comparison with spontaneous pregnancies, but also compared to other treatment options as Intra Uterine Insemination (IUI).
A spontaneous pregnancy and a naturally conceived pregnancy are used synonymously for the situations that a pregnancy occurred without fertility treatment. Although the expression naturally conceived pregnancy seems more appropriate, we used spontaneous pregnancy as this is most commonly used in the literature.

The NVOG (Dutch Society for Obstetrics and Gynaecology) developed a guideline IVF (www.NVOG.nl) indicating when referral for IVF of subfertile couples is justified. The guideline is based on different observational studies and consensus meetings. For the indications for IVF and ICSI treatment the different causes of subfertility are classified in the following categories: tubal pathology, endometriosis, hormonal and immunologic subfertility (including cervical hostility), male subfertility, and unexplained subfertility. The indication for IVF treatment is dependent on the cause of subfertility, the duration of subfertility in years, and on women's age. The guideline was updated for the last time in 1998. Validation and revision is recommended every 5 years. Meanwhile, IVF and ICSI treatments are established as full treatment options although most recommendations are still not evidence based.

Prognostic models

Ideally, a couple should only be referred for IVF treatment if the prospects of a spontaneous pregnancy are low and the chance on pregnancy would be considerably higher with IVF treatment. IVF treatment is an expensive, physically and emotionally burdensome treatment, with risks for complications, and should be withheld for couples with still a reasonable chance of a spontaneous pregnancy. Appropriate indication for IVF treatment for subfertile couples has been subject for research for many years and have lead to the development of several prognostic models predicting the probability of a spontaneous pregnancy in untreated couples (Eimers *et al.,* 1994, Collins *et al.,* 1995, and Snick *et al.,* 1997, Hunault *et al.,* 2004, van der Steeg *et al.,* 2007), as well as predicting the probability of pregnancy with IVF (Haan *et al.,* 1991, Templeton *et al.,* 1996, and Stolwijk *et al.,* 1996). The patient characteristics: women's age, the duration of subfertility and the pregnancy history (primary or secondary), appeared to be important predicting factors in both spontaneous and in IVF pregnancies.

Several draw-backs on models on the spontaneous pregnancy chance should be considered: the prognostic models for a spontaneous pregnancy are largely based on couples who have not been treated before. For the majority of women, prior to the start of IVF, some kind of treatment, mostly IUI, will have been performed. Since there is a couple-to-couple variation in pregnancy chances, couples with lower chances are more likely not to have conceived during previous treatment than couples with higher chances. For that reason the average spontaneous pregnancy rate for these couples waiting for IVF will be lower than in untreated couples and can not be compared with couples who have been referred directly by the general practitioner (as in the study of Snick *et al.,* 1997). In the study of Hunault *et al.,* 2002, the predictive value of a Dutch model with data from a tertiary setting (Eimers *et al.,* 1994,) was tested reasonable on the data of a Canadian study obtained from tertiary clinics as well (Collins *et al.,* 1995). On the other hand, prognostic models developed in tertiary clinics may not be applicable in a general Dutch fertility clinic.

The models for the prediction of the pregnancy chance with IVF (Haan *et al.,* 1991), have become outdated with the introduction of ICSI. Moreover, although important for its size, the Templeton model only predicted the pregnancy chance for one diagnostic category and one cycle of IVF (Templeton *et al.,* 1996). Furthermore, validation of the Templeton model in a Dutch academic IVF centre was unsatisfactory: only couples with a very low chance to conceive could be distinguished from couples with a very high chance (Smeenk *et al.,* 2000). To update the IVF guideline, there is a need of a prediction model for the pregnancy chance with IVF and ICSI treatment and a prediction model on the spontaneous pregnancy chances before treatment with prospectively collected national data.

After termination of IVF treatment, spontaneous pregnancies are still possible, both after successful and unsuccessful IVF treatment. Only a few studies, mostly on selective patient profiles are available on this subject (Cahill *et al.,* 2005, Ludwig *et al.,* 2008, Osmanagaoglu *et al.,* 2002). With the large OMEGA-dataset, a study on long-term health effects related to fertility treatment (Klip H. Thesis, 2002), we had an unique opportunity to study patient characteristics and lifestyle on the chance of spontaneous pregnancies resulting in a live birth for women who terminated IVF treatment.

Costs

The profit of a pregnancy with IVF should be balanced between the disadvantages of the costs and risks of treatment. Information about the actual costs of IVF treatment in the Netherlands is available, but cost estimates differ widely and the costs for ICSI were not separately assessed (Goverde *et al.,* 2000, Fiddler *et al*., 2006). For those reasons, detailed cost estimates should be gathered.
Next to direct costs, there are indirect costs e.g. originating from sick leave due to health related problems. Absence from work may result in productivity loss (Fiddler *et al.,* 2006), but only a part of the treatment cycle was covered in this study and the cause of absence from work was not available. If we would know to what extent physical and emotional complaints causes the absence of work by studying the predictors of absence of work, we might be able to prevent extremes.

Study

The Dutch Health Council indicated in 1997 that there is little evidence to support current IVF-practice and recommended an effectiveness study on IVF and ICSI treatment to find out for which couples, according to the subfertility cause, this expensive, physical and psychological burdensome treatment, is cost-effective (Gezondheidsraad, Herziening Planningbesluit 1997*).* In 2000, a cost-effectiveness study was published comparing IVF treatment with postponing IVF treatment, using the Templeton model for IVF and the Collins model for spontaneous pregnancies (Mol *et al.,* 2000). Because of the limited external validity of the used models in this study, there was still need of a cost-effectiveness study with randomized controlled data among subfertile couples, which should provide the tools for the appropriate indication for IVF or ICSI. A comparison between couples with an indication for IVF/ICSI, but not to be treated (yet), on one arm of the trial, and couples treated with IVF or ICSI on the other arm, would be ideal. For ethical and practical reasons, subfertile couples can not be

randomised to wait and hope for a spontaneous pregnancy when the treatment with IVF or ICSI, and therefore a presumably higher chance of pregnancy, will be offered to the other group. However, the disproportionate supply and demand for IVF seized the opportunity to use the waiting lists, which arose in the different IVF clinics, to mimic postponement of treatment as proposed in a randomised trial. This way, prospectively collected cohort data of couples on a waiting list before treatment were studied on the chance of a spontaneous pregnancy prior to IVF or ICSI treatment. Next, the pregnancy chance of couples finally starting IVF/ICSI after the waiting period, could be assessed. Comparison of pregnancies observed in both groups, those on a waiting list, and those treated, could than provide models on the prediction of pregnancies with and without treatment for couples of different diagnostic categories, to lead to more evidence on justified indication for IVF/ICSI.

Aims of the thesis

The main aim of the study was to assess the effect of different patient characteristics: women's age, pregnancy history (primary or secondary), cause and duration of subfertility on the outcome of IVF or ICSI in the Netherlands, and on the spontaneous pregnancy rates for couples on a waiting list before treatment. Additionally, the differences in pregnancy rate per IVF centre after controlling for patient mix were assessed.

We investigated the impact of other factors, such as lifestyle factors (smoking, body mass index (BMI), caffeine and alcohol use), on the pregnancy chance with IVF treatment and the spontaneous pregnancy chance after termination of IVF treatment.

Also the influences of psychological factors on the outcome of IVF/ICSI treatment were assessed and a screening tool to identify women at risk for emotional problems after unsuccessful treatment was investigated.

The direct and indirect medical costs of an IVF and ICSI treatment were calculated. Results were used in a cost-effectiveness analysis of IVF/ICSI for different diagnostic patient groups, at different durations of subfertility and at different age, compared to the chance of a pregnancy without treatment for couples with comparable profiles, when IVF/ICSI treatment was postponed.

Study design

All 13 Dutch IVF-centres agreed to participate to a national prospective cohort study on the evidence based indication of IVF and ICSI treatment. Over a two year period from 2002-2004, all new couples eligible for IVF or ICSI were put on a national "waiting list" before treatment. All centres started treatment according to their own waiting list and waiting period.

Subsequently, in 2004, the IVF/ICSI registries of 11 centres could be obtained, containing 5962 couples. The IVF registries were crosschecked with the couples on the national waiting list. For 4928 couples the data matched on both registries. These couples were followed from the start of treatment up until an ongoing pregnancy, or if a pregnancy did not occur, until 12 months after treatment start. For 1034 couples on the waiting list there was no match with the IVF registries. For these couples the medical files were searched by hand to find the reason why IVF/ICSI treatment had not taken place (yet). In case a spontaneous ongoing pregnancy had occurred during the waiting period before treatment (in 282 women), the subfertility related patient characteristics of the couples were determined.

During the national cohort study, a supplementary study among a subsample of women took place in 7 IVF clinics. Validated questionnaires assessing psychological factors were filled in by 783 women before a first IVF/ICSI treatment. A second and a third questionnaire had to be filled in before oocyte retrieval and several weeks after the pregnancy test. The IVF treatment outcomes of these women were obtained from the IVF registries. A daily diary about absence from work was kept by 411 women during the IVF/ICSI treatment up until 10 weeks after the start of treatment.

A large supplementary dataset of the OMEGA-project initiated in 1995 and carried out among 8457 women who retrieved IVF between 1983-1995, were used and provided information on lifestyle factors in relation to pregnancy with IVF. For 9669 women the influence on the spontaneous pregnancy chance after termination of IVF treatment was assessed.

During the cohort study of 2002-2004, the costs of a first IVF or ICSI treatment were investigated in 4 IVF centres and one transport clinic.

Finally two models predicting the pregnancy chance with IVF/ICSI and the spontaneous pregnancy chance while waiting on a list before treatment, were integrated with the costs of treatment, delivery and neonatal care, leading to a cost-effectiveness study of IVF/ICSI treatment for different patient groups.

The aim of this thesis is to answer the following questions:

1. What is the chance of pregnancy for couples starting IVF or ICSI treatment in the Netherlands?
2. Are there differences in pregnancy rate between IVF centres in the Netherlands?
3. What is the chance of a spontaneous pregnancy when IVF is postponed, and the chance of a spontaneously conceived live birth after termination of IVF treatment?
4. What is the impact of lifestyle factors on the pregnancy chance with IVF, and after termination of IVF?
5. What is the influence of psychological factors on the outcome of IVF/ICSI? Are emotional problems after unsuccessful IVF treatment predictable?
6. What are the costs of an IVF and ICSI treatment in the Netherlands?

Outline of the thesis

The first research question is answered in **chapter 2**. We described the results of a nationwide prospective cohort study of couples that were referred for IVF or ICSI treatment according to the Dutch IVF guideline. Subfertility related patient characteristics such as, women's age, pregnancy history (primary or secondary subfertility), cause and duration of subfertility, were analysed in a multivariate logistic regression model to predict the ongoing pregnancy chance within 12 months after the start of IVF or ICSI.

The second research question is investigated in **chapter 3**. We assessed the differences in ongoing pregnancy rates between 11 centres, while differences in patient mix and sample size variation were controlled for. For this analysis, the IVF and ICSI dataset from chapter 2 was used to compare the relative differences with the associated confidence intervals of the one-year ongoing pregnancy chance between the IVF centres.

The third research question is dealt with in chapter 4 and chapter 6. In **Chapter 4** we estimated the chance of pregnancy without treatment for couples eligible for IVF or ICSI, with prospectively collected data of couples entering a waiting list before treatment. A multivariate logistic regression analysis was used to relate patient characteristics to the spontaneous pregnancy chance of subfertile couples *before* IVF or ICSI treatment.

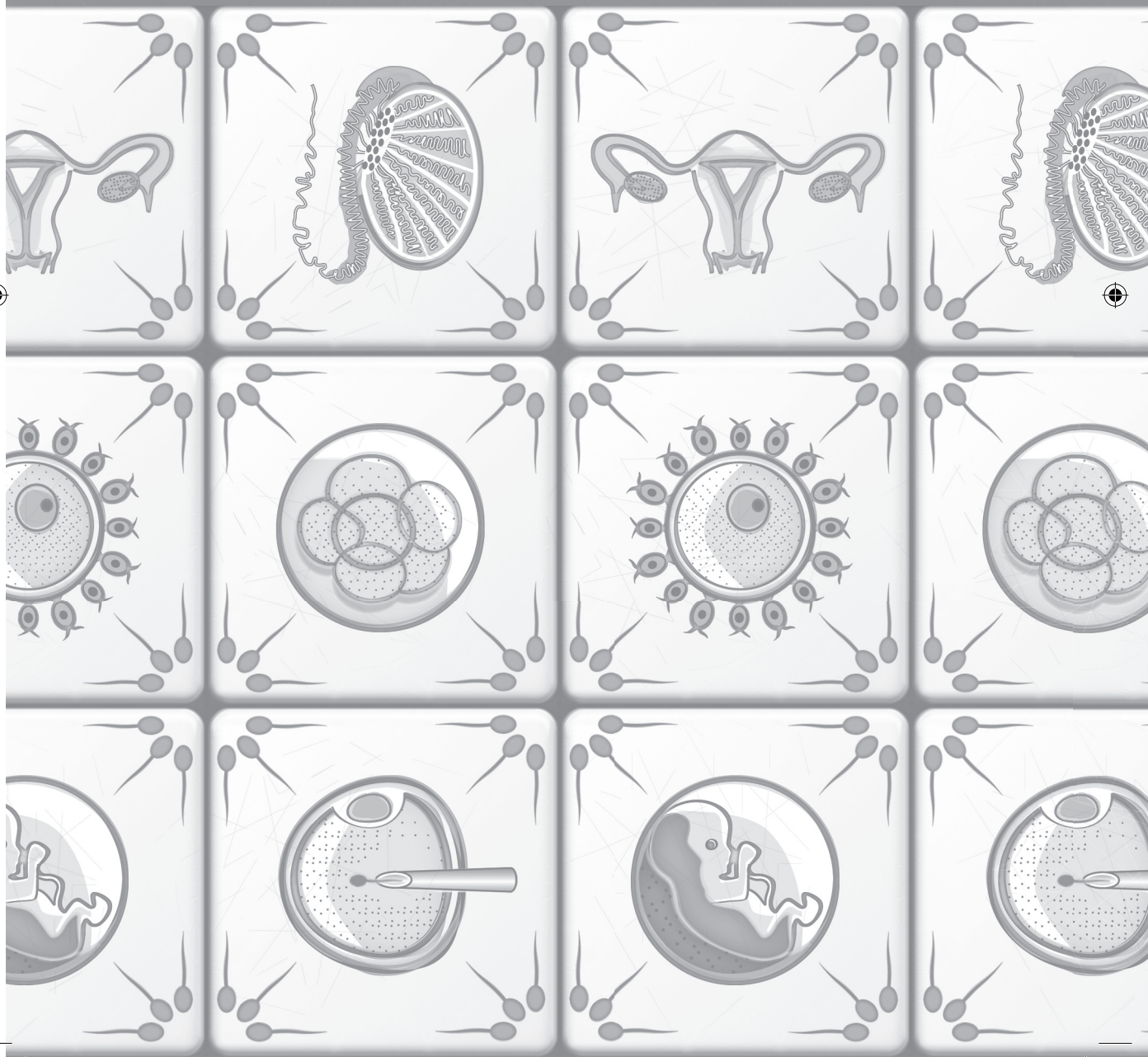
The fourth research question is evaluated in chapter 5 and chapter 6. In **chapter 5** we assessed the impact of smoking and body weight on the live birth rate with IVF treatment, in relation to subfertility related patient characteristics with a multivariate logistic regression analysis. We used data from a nationwide retrospectively collected cohort study, the OMEGA-project. In **chapter 6** we presented a model for the prediction of a spontaneous conception resulting in a live birth after termination of IVF treatment for the population in the OMEGA-cohort. The impact of lifestyle factors, subfertility related patient characteristics and prior treatment results was studied.

The fifth research question was investigated in chapter 7 and chapter 8. The influence of psychological distress before, during and after a first IVF or ICSI treatment was studied. Prospective data were collected by distribution of validated questionnaires in several IVF clinics. In **chapter 7** anxiety and depression levels were assessed and related to the cancellation and pregnancy rate with multivariate logistic regression analyses. Subfertility related patient characteristics were taken into account. In **chapter 8** we tested the predictive value of a new screening instrument for the development of emotional problems after IVF/ICSI treatment. The psychological dataset was matched with the IVF outcome data collected in chapter 2.

The sixth research question is studied in chapter 9, chapter 10 and chapter 11. In **chapter 9** we described the pattern and the average amount of absence from work during a first IVF/ICSI treatment cycle. The costs of productivity loss in women with paid work were estimated.

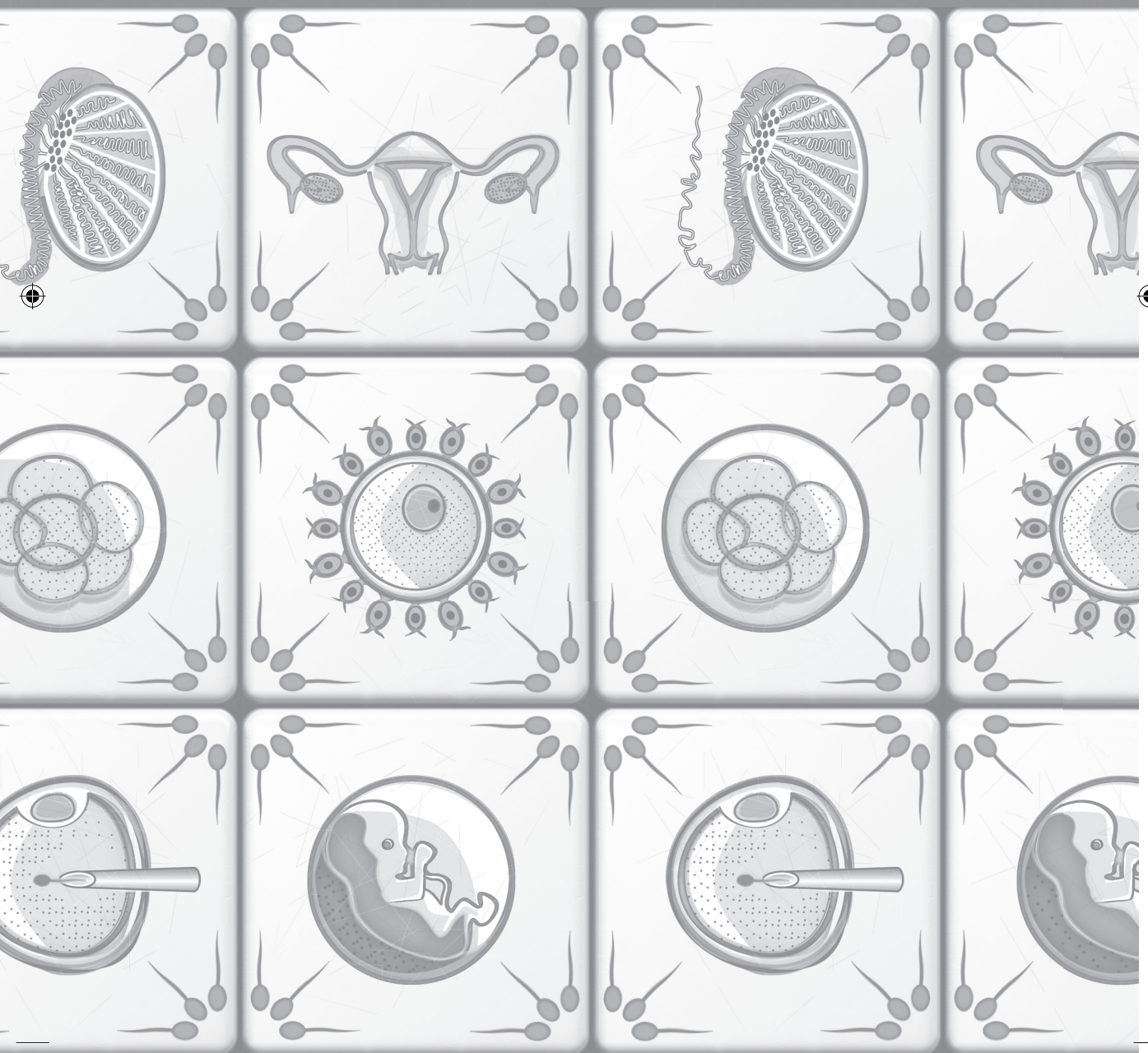
Additionally, the extent to which general and emotional factors contribute to absence from work was studied in a multivariate analysis. In **chapter 10** we determined the average, direct medical costs of a first IVF or ICSI treatment per treatment stage, per cycle and per ongoing pregnancy. Detailed cost data were collected on a representative sample of patients undergoing treatment in 5 IVF clinics until, if applicable, the first 8 weeks of pregnancy. In **chapter 11** we assessed the cost-effectiveness of starting IVF/ICSI according to the IVF guideline, compared to waiting one year longer, considering the predictive factors female age, duration of subfertility, pregnancy history and diagnostic category. The prospective cohort studies on chances of treatment-independent pregnancy (see chapter 4), and chances with IVF/ICSI of couples that did start treatment (see chapter 2), and costs estimates of IVF (see chapter 10) were integrated into a cost-effectiveness analysis.

In **chapter 12**, the results of the studies presented are discussed. The research questions of the thesis are answered, conclusions are drawn and recommendations given.



Part | I

Success rates



Chapter | 2

Predicting ongoing pregnancy chances after IVF and ICSI: a national prospective study

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Abstract

Background: The Dutch IVF guideline suggests triage of patients for IVF based on diagnostic category, duration of infertility and female age. There is no evidence for the effectiveness of these criteria. We evaluated the predictive value of patient characteristics that are used in the Dutch IVF guideline and developed a model that predicts the IVF ongoing pregnancy chance within 12 months.

Methods: In a national prospective cohort study, pregnancy chances after IVF and ICSI treatment were assessed. Couples eligible for IVF or ICSI were followed during 12 months, using the databases of 11 IVF centres and 20 transport IVF clinics. Kaplan-Meier analysis was performed to estimate the cumulative probability of an ongoing pregnancy, and Cox regression was used for assessing the effects of predictors of pregnancy.

Results: 4928 couples starting IVF/ICSI treatment were prospectively followed. On average couples had 1.8 cycles in twelve months for both IVF and ICSI. The 1-year probability of ongoing pregnancy was 44.8% (95% CI: 42.1%-47.5%). ICSI for severe oligospermia had a significantly higher ongoing pregnancy rate than IVF indicated treatments, with a multivariate Hazard Ratio (HR) of 1.22 (95% CI: 1.07-1.39). The success rates were comparable for all diagnostic categories of IVF. The highest success rate was at age 30, with a slight decline towards younger women and women up to 35 and a sharp drop after 35. Primary subfertility with a HR of 0.90 (95% CI: 0.83-0.99) and duration of subfertility with a HR of 0.97 (95% CI: 0.95-0.99) per year significantly affected the pregnancy chance.

Conclusions: The most important predictors of the pregnancy chance after IVF and ICSI are women's age and ICSI. The diagnostic category is of no consequence. Duration of subfertility and pregnancy history are of limited prognostic value.

Introduction

In 1983, In Vitro Fertilisation (IVF) was introduced in the Netherlands as a treatment for women suffering from bilateral tubal occlusion. Later on, couples with other reasons for subfertility were treated with IVF as well. With the development of ICSI in 1992, a new treatment option became available for couples with severe male subfertility.

As far as we know, the Netherlands are unique in the world for having a national guideline for starting IVF, which considers different diagnostic categories, age of the woman and duration of subfertility. All gynaecologists use the "IVF guideline" (Dutch Society for Obstetrics and Gynaecology, NVOG-Guideline no 09. 1998). The IVF guideline is based on prognostic models regarding pregnancy without treatment (Eimers *et al.*, 1994; Collins *et al.*, 1995; Snick *et al.*, 1997) and models regarding pregnancy after IVF (Haan *et al.*, 1991; Templeton *et al.*, 1996; Stolwijk *et al.*, 1996). The IVF models were developed on the basis of retrospectively collected data of selected populations. The largest study thus far was of Templeton *et al.* They studied factors as female's age, previous pregnancies, duration and cause of subfertility. Male causes were not included.

The IVF guideline has not yet been examined on prospectively gathered data. Additionally, there is a need for an update of the IVF guideline, since the overall IVF success rates have improved, and the models did not include ICSI. To evaluate the IVF guideline we planned to develop a model that predicts the ongoing pregnancy rate 12 months after the start of IVF or ICSI treatment, using data on patient characteristics and pregnancies. We initiated a study in which we prospectively evaluated the probability of pregnancy in relation to age of the woman, duration of subfertility, previous pregnancy history, and different diagnostic categories.
Most fertility studies present the IVF outcome per treatment cycle. However, what really matters for a couple is the outcome of the whole treatment. We will therefore notably concentrate on the ongoing pregnancy rate per couple treated, from the moment they start treatment up until one year later. For comparison with other studies, we also calculate the pregnancy rate per cycle.

Materials and Methods

From January 2002 until December 2004, a national prospective observational cohort study of IVF-patients was carried out in the Netherlands. In the present paper, we will focus on prognostic factors. All 13 Dutch IVF centres and all 23 IVF transport clinics agreed to participate in the study. In a transport IVF clinic, the couples are treated from the hormonal stimulation up to the ovum pick-up. Subsequently, the couple transports the follicle fluid containing the

oocytes to the laboratory of an IVF centre. The laboratory phase including the embryo transfer takes place at the IVF centre.
Two IVF centres and 3 transport clinics later withdrew from participation, because they were not able to meet the data requirements of the study.
All new couples consulting a gynaecologist in one of the IVF centres or transport clinics were included in the study if they had an indication for IVF (or ICSI) according to the IVF guideline (Dutch Society for Obstetrics and Gynaecology, 1998). Couples were treated according to the centre specific treatment protocols. Only cycles with "conventional" ovarian stimulation with gonadotrophins, combined with pituitary down-regulation through GnRH agonists or GnRH antagonists co-treatment, were included. The results of cycles with frozen embryo transfers were not used because many IVF treatment registries did not enclose this variable.
All IVF clinics are compelled to register their IVF treatments, but there is no central national registry of fertility treatments and the included patient characteristics may differ between clinics.

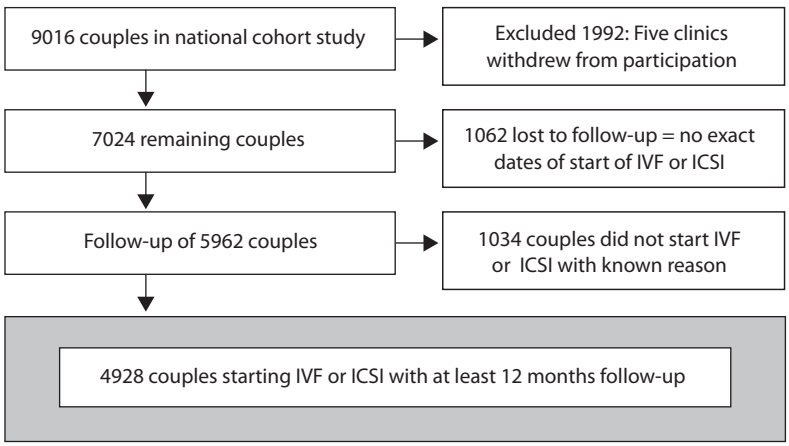
Patients

In the period of study, 9016 new couples with an indication for IVF or ICSI treatment consulted a gynaecologist. The couples that actually started IVF or ICSI were followed, from the date of last menstruation just before the first IVF treatment up until at least 12 months in case no pregnancy occurred. In case of pregnancy, follow-up continued until an ongoing pregnancy was confirmed by ultrasound (≥8 weeks gestation). For pregnancies ending in a spontaneous abortion, follow-up continued until an ongoing pregnancy occurred or otherwise at least for 12 months. For 4928 new couples, we were able to do a complete follow-up from the start of IVF or ICSI until at least 1 year. Figure 1 shows the flow diagram from all patients originally included in the study, to those used in the analysis.

Indication

Whether couples are indicated to start IVF or ICSI treatment according to the IVF guideline depends on the cause and duration of subfertility, and on women's age. Six diagnostic categories for IVF are considered. When the subfertility is caused by pathology of the tubal function, such as 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), IVF is only indicated after a duration of subfertility of at least three years and should be preceded by intra uterine insemination (IUI). Minimal endometriosis is treated as unexplained subfertility (3). In case of ovulation disorders, mainly caused by polycystic ovary syndrome (PCOS) (4), at least twelve 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 two years and is preceded by IUI. An identical advice applies for mild male oligospermia

Figure 1 Flow diagram of all patients included in this study



(6): if the multiplication of the volume, concentration and motility (VCM) of the semen after analyses is between 1 and10 million, IVF is offered after at least two years of subfertility and unsuccessful IUI. For severe oligospermia (VCM < 1 x 10^6), 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 years or 38 years, respectively. There is no upper age limit mentioned, but the guideline advises not to treat women over 40 years of age, because of poor treatment outcome. The guideline for IVF is developed for primary subfertility. One recognises that women with secondary subfertility are somewhat different, but this is not taken into account in the guideline.

Definitions

In case of total fertilisation failure, or if only 10 % or less of the oocytes are fertilized, IVF treatment may be changed into ICSI in the next cycle. When the first cycle was an IVF cycle, the couple was included in the category "IVF", regardless whether later they changed into ICSI treatment. Primary subfertility indicates that the woman had no pregnancy before. Duration of subfertility is defined as the time between the date of active child wish, or the date of last miscarriage or delivery date, and the date of first IVF. The end point of the study was ongoing pregnancy, defined as a pregnancy with heartbeat of one or more foetuses confirmed by ultrasound, at 8 weeks gestation. Ongoing twin pregnancy was defined as a pregnancy with heartbeat of two foetuses.

Prognostic variables

Prognostic variables found to be important in previous studies were analysed: women's age, duration of subfertility, pregnancy history (defined as primary or secondary subfertility of the woman treated), and all diagnostic categories of IVF, being tubal pathology, unexplained subfertility, mild male, hormonal, cervical or immunological subfertility and endometriosis. In addition ICSI treatment, applied in case of severe oligospermia, was included as a separate category.

Data analyses

We used Kaplan-Meier analysis to estimate the cumulative probability of ongoing pregnancy after IVF or ICSI. If couples dropped out of the IVF programme within 12 months, their follow-up time was allowed to continue until 12 months assuming that they had no chance of pregnancy, so no censoring was applied (Daya 2005).

In addition, we analysed the cumulative probability of ongoing pregnancy against cycle number. This analysis was done twice, once with the usual censoring of patients who stopped treatment without pregnancy (giving the *potential* cumulative curve) and once with censoring as described above, giving the *realistic* cumulative curve (Stolwijk *et al.*, 2000). In the sequel, we will often drop the adjective "cumulative" for brevity.

Multivariate Cox regression analysis was used to estimate the predictive effect of the following prognostic variables on the probability of ongoing pregnancy: age of the woman, duration of subfertility, diagnostic category and whether the woman's subfertility was primary or secondary**.** To check for a non-linearity of the effect of the woman's age, a restricted cubic spline curve was used (Harrell *et al.*, 1988), with 5 knots at ages 23, 27, 32, 37 and 42 years.

To assess the internal validity of the resulting prediction model, the bootstrap method was used with 200 replications. The optimism corrected c-statistic was assessed, which is equivalent to the ROC curve (AUC), to measure how well the model is able to make a distinction between pregnant and non-pregnant couples ('discrimination'). Further, the bootstrap method assesses whether the pregnancy chances predicted by the model are reliable, i.e. whether they agree with the observed proportion of pregnant couples ('calibration').

The results of the Cox regression were converted into a ready-to-use score chart that may be used by clinicians to calculate the chance of an ongoing pregnancy within one year for a given couple.

Missing data occurred in women's age (0.7%), duration of subfertility (6.4%), pregnancy history (6.4%), diagnostic category (6.9%), outcome of IVF treatment (pregnant or not) (3.8%) and whether a registered pregnancy was ongoing or not (7.0%). These missing items were imputed to avoid the loss of data in multivariate analysis and to avoid potential bias. For this purpose, single imputation with the AregImpute method in S-plus (MathSoft. Inc., Seattle, WA, version 2000) was used.

Results

Table I gives the characteristics of the 4928 couples starting IVF or ICSI in one of the 11 IVF centres or 20 transport clinics in the Netherlands, subdivided by diagnostic category. The mean age of the women at the beginning of the treatment was 34.0 years (SD = 4.0) for IVF and 32.6 (SD = 4.2) for ICSI. The mean number of cycles in twelve months was 1.8 for both IVF and ICSI. The overall 1-year ongoing pregnancy rate was estimated to be 44.8% (95% CI: 42.1-47.5%) (the upper panel of Figure 2). The ongoing pregnancy chances for couples who will sustain treatment for four cycles are as high as 63 %, whereas the realistic chances after the fourth cycle are only 42%, (the lower panel of Figure 2).

In Table II, univariate results of the effect of patient characteristics on the ongoing and twin pregnancy rates are shown. With increasing female age, both rates decreased significantly. For women under 25, the effect was different. In fact the relationship between age and pregnancy chance was non-linear ($p < 0.001$, Figure 3), with the highest chance at age 30 and a slight decline towards younger and older women up to age 35. After 35, the pregnancy chance sharply decreased. The curve shown in Figure 3 was calculated for one specific patient profile: women with primary unexplained subfertility with a duration of ≥ 3 years. The shape of this curve did not depend on the duration of subfertility, pregnancy history and diagnostic category (all tests for interaction had $p > 0.05$). Thus the level of the curve will differ between patient profiles, but not the shape.

Table I Characteristics of 4928 couples starting IVF or ICSI treatment during 2002-2004 in the Netherlands

Diagnostic category	Number of women	Age of the woman (years)		Duration of subfertility (years)		% Primary infertility
		Mean	SD	Mean	SD	
Tubal pathology	837	34.5	4.0	3.6	2.6	50
Unexplained	891	34.8	3.9	4.0	2.1	59
Male mild (IVF)	709	33.6	4.2	3.7	2.1	69
Male severe (ICSI)	1265	32.6	4.2	3.3	2.2	66
Endometriosis	410	32.8	3.8	3.3	1.9	71
Hormonal	353	33.2	3.9	3.7	2.1	63
Immunological	124	34.4	4.1	3.8	2.4	61
Missing	339	32.8	4.3	3.6	1.8	73
Total	4928	33.6	4.2	3.6	2.2	63

Figure 2 Overall 1-year ongoing pregnancy rate (upper panel) and ongoing chances for couples with respect to the number of cycles (lower panel)

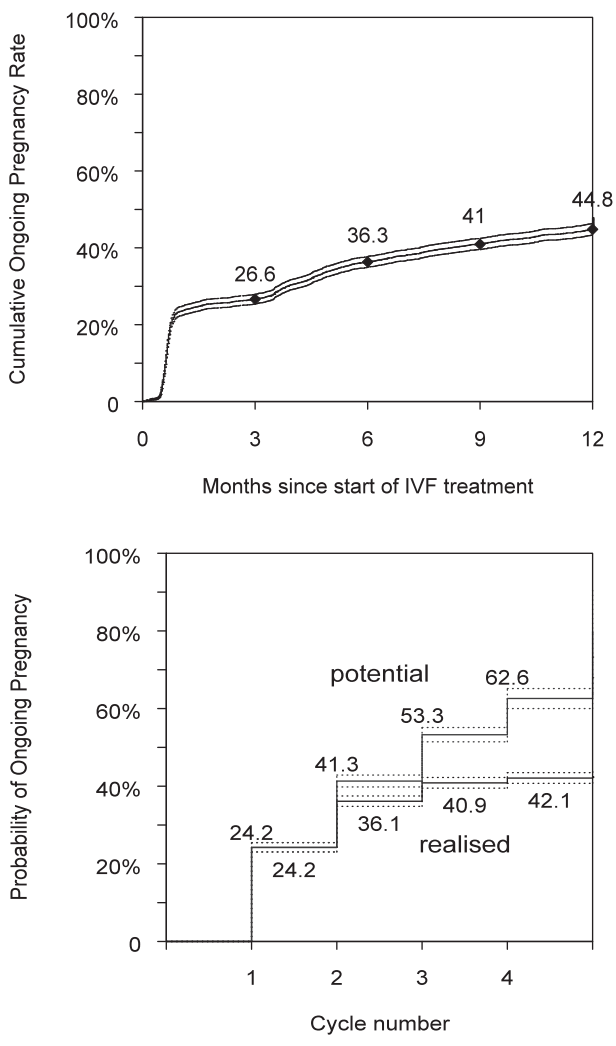
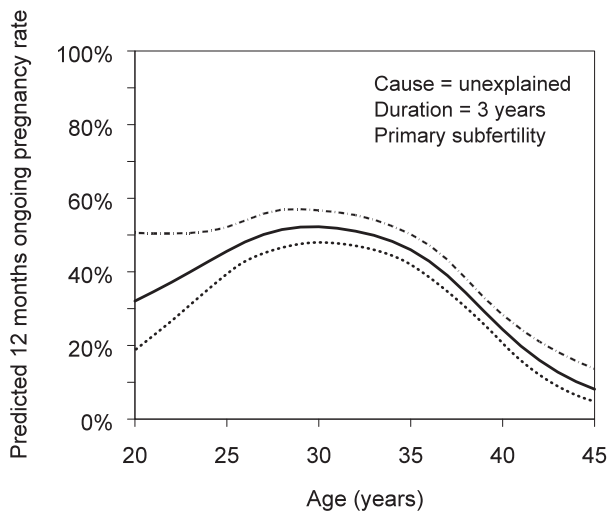


Table II The 1-year ongoing pregnancy rate (PR) and twin pregnancy rate, according to woman's age, duration of subfertility, the pregnancy history and the diagnostic category. Univariate analysis

	Number of Women	Number of cycles within 1 year (mean)	P-value	Cumulative ongoing P.R. (%)	P-value	Ongoing twin P.R. (%)	P-value
Age			< 0.001		< 0.0001		0.003
20-24	106	1.7		39		27	
25-29	838	1.7		52		29	
30-34	2,134	1.7		50		22	
35-39	1,539	1.9		38		15	
40-44	276	1.9		24		11	
Duration of subfertility			0.15		0.09		0.9
< 2 years	954	1.8		46		22	
2-3 years	1,086	1.8		48		21	
3-4 years	1,070	1.8		45		21	
4-6 years	1,006	1.7		42		23	
≥ 6 years	496	1.8		41		20	
Pregnancy history			0.007		0.6		0.9
Primary	2,898	1.8		44		22	
Secondary	1,716	1.7		45		22	
Diagnostic category			0.07		0.001		0.9
Tubal	837	1.8		41		22	
Unexplained	891	1.8		43		20	
Male mild	709	1.8		45		26	
Male severe (ICSI)	1,265	1.8		51		20	
Endometriosis	410	1.8		46		21	
Hormonal	353	1.8		46		22	
Immunological	124	1.9		36		17	
Total		1.8		45		22	

Figure 3 Relationship between age and pregnancy chance



With an increasing duration of subfertility there was a trend of decreasing pregnancy rate, but no effect on the twin rate. Pregnancy history did neither influence the pregnancy rate, nor the twin rate. There were significant differences between the different diagnostic categories: severe oligospermia with ICSI gave the highest pregnancy chances and immunological and tubal pathology the lowest ones.

In Table III, the results of the multivariable Cox regression model are shown. The impact of woman's age is presented in Hazard ratios compared to the age 35. For example, a woman of 38 has a 28% lower chance to become pregnant in 1 year IVF-treatment, compared to a woman of 35. Age, duration of subfertility and pregnancy history had a statistically significant effect. The chance of pregnancy did not differ between diagnostic categories for IVF. In case of ICSI, for severe male subfertility couples had a 22% higher ongoing pregnancy chance.

The c-statistic, measuring the discriminative ability of this model, was 0.583 and 0.577 after correction for optimism. Calibration was very good, the correction factor needed to make the model predictions agree with observations was 0.94, i.e. very close to unity (= no correction necessary), (Harrell *et al.*, 1996).

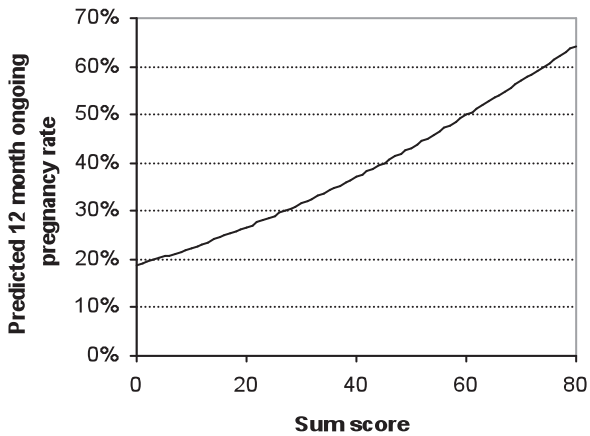
Table III Multivariable analysis with HRs for ongoing pregnancy with IVF and ICSI

Age (years)	HR	95% CI	P-value <0.0001
25	0.99	0.83-1.18	
27	1.14	0.98-1.32	
29	1.21	1.08-1.35	
31	1.20	1.14-1.28	
33	1.14	1.12-1.16	
35[1]	1		
37	0.82	0.75-0.91	
38	0.72	0.64-0.80	
39	0.58	0.51-0.66	
40	0.46	0.39-0.54	
Duration of subfertility (per year)	0.97	0.95-0.99	0.01
Primary subfertility	0.90	0.83-0.99	0.03
Diagnostic category			0.11
Tubal pathology[2]	1	--	
Unexplained	1.10	0.95-1.27	
Male mild	1.06	0.91-1.24	
Male severe (ICSI)	1.22	1.07-1.39	
Endometriosis	1.05	0.88-1.26	
Hormonal	1.07	0.89-1.30	
Immunologic/cervical subfertility	1.04	0.78-1.40	

[1] Hazard ratios for age are expressed relative to a reference age of 35 years.
[2] Tubal pathology was taken as the reference category.

In Figure 4, a score chart is presented that may be used to calculate the predicted ongoing pregnancy rate for a given couple. For example, a couple with female age of 39 years (11 points), duration of infertility of 4 years (11 points), a regular indication for IVF (0 points) and primary infertility (0 points) has a sum score of 22 points and therefore a prospect of achieving an ongoing pregnancy within a year from start of IVF treatment of 28%, as can be read from the curve. Had the woman instead been 29 years (49 points), the sum score would have been 60 points and the predicted pregnancy chance 50%.

Figure 4 Score chart with corresponding curve to calculate the 12-months predicted ongoing pregnancy rate for a patient of a given age, indication, duration and type of infertility



Age	Points	Duration	Points	Treatment modality	Points	Type of infertility	Points	
25	39	1	15	IVF	0	Primary	0	
26	43	2	14	ICSI	7	Secondary	6	
27	46	3	12					
28	48	4	11					
29	49	5	10					
30	49	6	8					
31	48	7	7					
32	47	8	5					
33	45	9	4					
34	43	10	3					
35	40	11	1					
36	35	12	0					
37	29							
38	20							
39	11							
40	0							Sum score:
	…		…		…		…	…

Discussion

This large prospective study on prognostic factors predicting the chance of pregnancy with IVF is the first one, in which all diagnostic categories that are considered in the IVF guideline are studied. The most important predictive factor is women's age. Duration of subfertility, and pregnancy history are also of concern for the couple's prospect of achieving a pregnancy with IVF or ICSI. Both in univariate and in multivariate analyses, the effects of duration of subfertility, pregnancy history and diagnostic category are modest. Only for women older than 35, pregnancy chances become much lower, and for ICSI, in case of severe oligospermia, chances are higher than for IVF. The chance of pregnancy for other categories is not very different from the chance for tubal pathology, the IVF indication par excellence.
We think that the pregnancy rate with ICSI is not higher because of the technical procedure see also Bhattacharya *et al*., 2001, but because women selected for ICSI have themselves, in most cases, no factor of subfertility. The ICSI indication is indeed primarily due to the severe fertility problem of their partner. This does not explain the lower twin rate for this group. Presumably these women more often had elective single embryo transfer; unfortunately we could not check this in our data.

We emphasize that after 35 the pregnancy rate strongly declines. In this respect, the IVF guideline advises not to treat women over 40 because of poor treatment outcome. However, in our sample, women in the oldest age group (40-45) had a fair 1-year ongoing pregnancy chance of 24%. Probably, women over 40 with positive prospects were selected by pre-screening of the ovarian reserve by ultrasound based antral follicle count and serum basal follicle stimulating hormone (Klinkert *et al*., 2005).

It seems contradictory that women in the youngest age group (< 25 years) had lower pregnancy rates than women in the subsequent age group, but Templeton *et al*. (1996) and Human Fertilisation and Embryology Authority data (NICE guideline 2004) showed a similar trend for live birth rates per cycle for this age group. Despite the relatively small number of patients in this age group, this repeated finding suggests that it may be a real phenomenon, not a chance finding. The relationships between child wish at young age, lower social class and detrimental lifestyle habits such as smoking and overweight may be the reason for the lower pregnancy rate.

The IVF guideline advises on when to start IVF, depending on the diagnostic category. This advice is based on prognostic models for pregnancy chances without treatment (Collins *et al*., 1995, Snick *et al*., 1997). For couples with unexplained subfertility, the spontaneous

conception rate during the first three years of subfertility is substantial (Pandian *et al.*, 2005). Therefore, the advice is to wait at least three years before starting IVF treatment. We found that the overall cumulative ongoing pregnancy rate with IVF for couples with unexplained subfertility is comparable with the pregnancy rate of other diagnostic categories, which according to the guideline, can be treated sooner. This means that the differences in duration of subfertility as formulated in the Dutch IVF guideline are probably appropriate. Whether unexplained subfertility can be seen as a separate diagnosis is under debate (Gleicher and Barad, 2006). It is most likely a mixture of potentially good prognosis couples and women with a low chance to become pregnant e.g. because of imminent premature ovarian failure. It would be ideal if we were able to differentiate for unexplained subfertility, between couples with a fair chance and couples with a low chance of conception without treatment. We would then be able to counsel individually when to start IVF, or maybe sometimes to advise not to start treatment at all.

The fertility treatment history of a patient is also of importance for the overall IVF treatment outcome. Before starting IVF, ovulation induction or ovarian hyperstimulation and/or IUI will be the main treatment options. Only the unsuccessful couples, probably a selection with lower pregnancy chances, are referred for IVF. Regrettably, we do not have data on the treatment history and can only suppose that the patients in our study were referred for IVF according to the IVF guideline and that in case of mild male, hormonal and unexplained subfertility, the conventional treatments had preceded IVF.

We compared our results with those of Templeton *et al.* (1996). The impact of duration of subfertility was comparable. They found that only after a very long duration of subfertility (>13 years), the impact on the IVF-pregnancy chance is substantial. However, we did not have couples with such an extreme duration of subfertility. It was difficult to compare the value of pregnancy history. Since we did not have detailed information on the previous pregnancy, we could only distinguish between primary and secondary subfertility. According to Templeton *et al.* (1996) and Stolwijk *et al.* (2000) it is of supplementary prognostic value if the previous pregnancy has led to life birth and if this life birth has been due to IVF. Diagnostic categories cannot be compared as Templeton *et al.* had only tubal pathology in their model.

In the period of our study, the first three IVF treatments were reimbursed by health insurance. Economic reasons for delaying or dropping out of the programme are therefore not plausible. The reason for dropping out is often related to the outcome, although earlier research is contradictory (Roest *et al.*, 1998, de Vries *et al.*, 1999, Smeenk *et al.*, 2004). We assigned a zero probability of pregnancy to couples that discontinue treatment, see Daya (2005). The resulting

curve is the one that couples should expect when they start treatment. We named this curve "realistic" instead of "pessimistic" (Stolwijk *et al.,* 2000), as it represents what really happened, and therefore what is relevant for patients. Because patients might also want to have information on the cumulative chances after a given number of cycles, we made a separate curve of the cumulative chances against cycle number, in which dropouts are censored. This curve gives chances that could potentially be realised, given that a patient is able to sustain treatment for that number of cycles. We were not able to correct this curve for informative censoring, so the predicted chances will be too optimistic (Stolwijk *et al*., 2000).

Lifestyle like smoking, body weight, and psychological factors influence the outcome of IVF (Klonoff-Cohen 2005, Lintsen *et al*., 2005, Smeenk *et al*., 2001), but are not investigated in this study.

Unexpectedly, most registers we received did not include an accurate registration of the cryopreserved embryos. We regret that the lack of the relevant information of pregnancies obtained from frozen embryos could not be included in the model, although according to de Jong *et al*., 2002, the supplementary pregnancy chances by using cryopreserved supranumerical embryos are of limited size.

Five IVF clinics did not deliver their IVF treatment registries. The Dutch society of Obstetricians and Gynaecologists website (www.NVOG.nl) reports on the number of IVF and ICSI treatments and the average ongoing pregnancy rate of every IVF centre. These results are not on an individual level and could therefore not be used in our analyses. Using the per centre information we could conclude that the results of the missing clinics were in the same range as the included clinics and that their dropout therefore will not have biased our results.

Over 1000 women were lost to follow-up because of incomplete or sometimes incompatible registration files. To carry out a large prospective study as we did, a national registration of all fertility treatments is ideal. Only compelled uniform registration, can overcome the problem of loss.

The advantage of the present study in relation to earlier research is that the analyses were based on complete data with a long follow-up, and that, next to results per cycle, we also analysed the results per woman/couple treated. The pregnancy chances are therefore easier to interpret for counselling. Contrary to others (Dor *et al*., 1996; Stolwijk *et al*., 1996; Templeton *et al*., 1996; Hunault *et al*., 2002), we studied all causes of subfertility and both IVF and ICSI. A clear description of diagnostic categories and restriction of treatment to couples that comply with the IVF guideline, has led to a well-defined group of couples with subfertility.

In the present study we estimated the predictive value of patient characteristics on pregnancy chances with IVF and ICSI. Female age has an eminent influence on the pregnancy prospect of a couple. The woman's pregnancy history and the duration of subfertility have a modest but significant effect on the ongoing pregnancy chance. The diagnostic category does not influence the pregnancy chance, except for severe male subfertility treated with ICSI. With these patient characteristics, we developed a prognostic model to predict the cumulative ongoing pregnancy chance within one year after the start of treatment.

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2

Chapter | 3

3

Can differences in IVF success rates between centres be explained by patient characteristics and sample size?

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Abstract

Background: Pregnancy rates cannot be used reliably for comparison of IVF clinic performance because of differences in patients between clinics. We investigate if differences in pregnancy chance between IVF centres remain after adjustment for patient mix.

Methods: We prospectively collected IVF and ICSI treatment data from 11 out of 13 IVF centres in the Netherlands, between 2002 and 2004. Adjustment for sampling variation was made using a random effects model. A prognostic index for subfertility-related factors was used to adjust for differences in patient mix. The remaining variability between centres was split in random variation and true differences.

Results: The crude 1-year ongoing pregnancy chance per centre differed nearly a factor 3 between centres, with hazard ratio's (HRs) of 0.48 (95% CI: 0.34-0.69) to 1.34 (95% CI:1.18-1.51) compared to the mean 1-year ongoing pregnancy chance of all centres. After accounting for sampling variation, the difference shrank since HRs became 0.66 (95% CI:0.51-0.85) to 1.28 (95% CI: 1.13-1.44). After adjustment for patient mix, the difference narrowed somewhat further to HRs of 0.74 (95% CI: 0.57-0.94) to 1.33 (95% CI: 1.20-1.48) and 17% of the variation between centres could be explained by patient mix. The 1-year cumulative ongoing pregnancy rate in the two most extreme centres were 36% and 55%.

Conclusions: Only a minor part of the differences in pregnancy chance between IVF centres is explained by patient mix. Further research is needed to elucidate the causes of the remaining differences.

Introduction

Since 1996, reports on the ongoing pregnancy rate per IVF and ICSI treatment are publicly available for all 13 IVF centres in the Netherlands. The National Infertility Registration (LIR, www.lirinfo.nl), publishes the annual ongoing pregnancy rates per started cycle, per embryo transfer after cryo-preservation, and the number of multiple pregnancies per IVF centre. Confidence intervals of the ongoing pregnancy rates per centre indicate the year-to-year variety caused by chance alone. Variability in characteristics of patients treated (patient mix) may explain systematic differences in pregnancy rate per centre. Information on patient mix, and on the proportion of elective single embryo transfer (eSET), is lacking in the LIR survey. Thus, for several reasons, the pregnancy results of the Dutch IVF centres cannot be compared directly.

Since the early years of IVF in the Netherlands, the success rates per centre have been subject of interest (Haan *et al*., 1991, Kremer *et al*., 2002, 2008, Lemmers *et al*., 2007). Haan *et al*. (1991), adjusted for a standardized good prognosis group, but differences in pregnancy rates between the five centres studied remained. In the UK, Marshall and Spiegelhalter (1998) ranked 52 IVF centres in a league table after adjustment for patient mix. There were wide confidence intervals for the ranks associated with the pregnancy rate, in particular for the small-sample-sized clinics, leading to the conclusion that the usefulness of ranking is questionable. Castilla *et al*. (2008) compared different graphical classification methods of IVF clinics on crude IVF data of 58 IVF clinics in Spain. The relative differences between IVF clinics were dependent on the method used, which again limits the value of ranking.

The situation for IVF clinics in the Netherlands differs from the UK and other European countries in several respects. In the Netherlands there are no private or really small clinics and there is a national guideline in which duration and cause of subfertility, pregnancy history and women's age determine the moment of referral for IVF. The uniform circumstances in which the Dutch IVF centres operate suggests that the real inter-centre differences in pregnancy chance between centres can be measured after adjustment for patient mix and sample variation. The purpose of this study is to examine if differences in pregnancy rates between IVF centres remain after controlling for the variation in patients treated.

Material and Methods

Patients and prognostic variables

From January 2002 until January 2004, a national cohort study on the prediction of pregnancy of subfertile couples was carried out in 13 IVF centres in the Netherlands. Prospectively, subfertile couples starting a first IVF/ICSI treatment were registered on a national waiting list.

During 2004, the waiting list was cross-checked with the IVF treatment registries of the IVF centres. Only couples that actually started IVF treatment during this period were included in this study. The purpose of the national cohort study was bipartite: first to estimate the chance of pregnancy without treatment for couples on the waiting list before IVF (Eijkemans *et al.,* 2008) and second to predict the ongoing pregnancy chance of a couple within 1-year after the start of IVF or ICSI treatment (Lintsen *et al.,* 2007).

Although there is no uniform registration, IVF centres are compelled to register the following items: the number of IVF treatments started, the outcome until ongoing pregnancy (pregnancy with fetal heartbeat confirmed by ultrasound after at least 8 weeks gestation) and patient characteristics such as women's age, the duration of subfertility, pregnancy history before IVF (primary or secondary subfertility) and the diagnostic category. Two out of 13 centres were not able to deliver their IVF registries during the study period.

If couples failed to conceive after the first treatment, subsequent treatments were counted up until 1 year after the start of treatment. Per couple, the mean number of IVF cycles performed within 12 months was 1.8. If couples discontinued treatment they were considered to have no chance of pregnancy, as drop-outs are often related to the prospect of treatment (see the ´realistic" approach Lintsen *et al.,* 2007). For the majority of treatments, the pituitary down-regulation was carried out in a long protocol and preceded the ovarian stimulation with gonadotrophins. A maximum of two embryos (double embryo transfer, DET) was carried out by all centres. During the study period, eSET was not a common option of treatment. The registration of the number of embryos transferred per cycle and the number of frozen embryo transfers was incomplete, we therefore assumed DET for every cycle and did not include cycles with cryo preserved embryos.The average ongoing pregnancy rate for all participating clinics, after the first cycle was 24%, the overall ongoing pregnancy rate within 1 year of treatment was 45% (for further details see Lintsen *et al.*, 2007).

The indication for IVF or ICSI is described in six diagnostic categories in the guideline IVF (Dutch society for Obstetrics and Gynaecology, NVOG guideline no. 09, 1998): With both sided tubal occlusion or with severe male subfertility, to be treated with ICSI, couples can be referred immediately. In case, no cause of subfertility is found, the chance of a spontaneous pregnancy is estimated to be high enough to justify postponement of IVF for the first three years of subfertility and should be preceded by intrauterine insemination (IUI). When the woman is 36 years old, IVF is indicated 1 year earlier, and even sooner when she would otherwise reach the age of 40. For endometrioses, the minimum subfertile period before referral for IVF depends on the severity of the pathology. With hormonal disturbances, IVF is indicated after repeated attempts of ovulation induction. With cervical hostility, and mild male subfertility, IUI is the first

treatment option and has to precede IVF. The guideline has no absolute age limit, but gives an emphatic advice not to treat women over 40 years of age.

The following fertility related prognostic variables on the 1-year ongoing pregnancy rate in IVF and ICSI treatment were studied in a multivariate prediction model in Lintsen *et al.* (2007): women's age, pregnancy history, duration and cause of subfertility. The 1-year ongoing pregnancy rate decreased with older age and increasing duration of subfertility, was lower for women with a primary subfertility compared to those with secondary subfertility, was independent of the cause for IVF treatment, but was higher for couples primarily treated with ICSI because of severe male subfertility. We used the same variables as used in the prognostic index, but estimated the coefficients for the models in this paper once again, for each centre separately and compared the 1-year ongoing pregnancy chance to the mean chance of all centres.

After crosschecking the IVF databases with the waiting list, we included those couples that matched on both registries. The period on the waiting list differed per centre. For IVF centres with a long waiting list, the period of matching couples was shorter compared to centres with a short waiting time. This varied between centres from 3 to16 months. For this reason, the number of patients per centre included in the study did not correspond with the actual size of the centre.

For the interpretation of the uncertainty of the results, sample size is of importance. Smaller samples can more easily take on extreme values because of sampling variability. In a new sample (e.g. data from a following year), the value is likely to be less extreme, the well known phenomenon of regression to the mean (Bland and Altman, 1994). Random-effects models (Laird and Ware, 1982) implicitly account for this fact by shifting results from small clinics to the overall mean. A test for proportional hazards was performed on the scaled Schoenfeld residuals as described previously (Grambsch and Therneau, 1994).
In agreement with the study protocol the IVF centres are compared while anonymity of the centres is preserved.

Data analyses

Patient characteristics per centre were presented in categories and differences between centres tested by chi-squared tests. Adjustment for patient mix was established by Cox regression, with the prognostic factors female age modeled as a restricted cubic spline with knots at ages 23, 27, 32, 37 and 42, duration of subfertility as a linear effect, and diagnostic category and primary versus secondary subfertility and the centres as a categorical variable. The relative differences of the 1-year ongoing pregnancy chance between the centres were expressed in hazard ratio's (HRs) with the associated confidence intervals (CI) and compared to the mean 1-year ongoing pregnancy chance of all centres during the study period, using

classical sum contrasts for the centre variable. The intervals indicate the margin of uncertainty about the estimated relative pregnancy rate. Random-effects analysis was performed with a normal distribution assumption for the between-centre variation in log-HR and produced an estimate of the variance. The differences in the estimates of the random effects variance between an unadjusted model and an adjusted model is a measure of variation explained by differences in patient mix. The Coxme function was used in R version 2.6.2

Missing data occurred in on average 5% of the following variables, women's age, duration of subfertility, pregnancy history, diagnostic category, outcome IVF (pregnancy or not), and whether the pregnancy was ongoing or not. Single imputation with the AregImpute method in S-plus (MathSoft Inc., Seatle, WA, version 2000) was used to avoid the loss of data.

Results

The 1-year ongoing pregnancy rates of 4928 couples starting IVF and ICSI treatments from 2002 to 2004 were analysed per IVF centre. The distribution of patient characteristics per centre are presented in Table I. The range for women < 30 years of age was from 15% to 25%, for women ≥ 35 from 29% to 54 %. The range of couples with a relatively short duration of subfertility < 3 year was from 35% to 59% and for a long duration of subfertility ≥ 6 year was from 6% to18%. Centres differed in the percentage of couples with a primary subfertility ranging from 57% to72%. The range per centre for ICSI treatment was from 19% to 59%. The differences in patient mix between centres were statistically significant with $p < 0.001$. Table II presents in column A the crude HRs per centre with the associated 95% CI, of the ongoing pregnancy chance per couple after 12 months of treatment, compared to the mean chance of the centres. The results after accounting for sampling variation are shown in column B, and subsequently adjusted for patient mix, in column C. The matching figures (Figure 1) give a graphical representation of the estimates. The size of the spot corresponds to the size of the sample, but not with the actual size of the centre. The unadjusted HRs demonstrate a significantly low relative pregnancy chance for centre no. 1, HR 0.48 (95% CI: 0.34-0.69) and relative high pregnancy chances for centres no. 4, 3, 10 and 11 with HRs 1.34 (95% CI: 1.18-1.51), 1.30 (1.10-1.54) 1.29 (CI: 1.16-1.44) and 1.13 (CI: 1.01-1.26), respectively. After accounting for the sampling variation the estimates with their CIs shrunk towards the mean for most centres. Then after adjustment for patient mix, the relative 1-year ongoing pregnancy rates raised for centre no. 1, 2, and 10. This means that these centres have treated relatively more patient with a poor prognosis. The rates decreased for centre no. 3, 4, 5, 7, 8, and 9 after adjustment of patient mix, which suggests that they treated relatively more good prognosis patients. Finally, the lowest estimates were for centre no.1 and 8, with HR 0.74 (95% CI 0.57-0.94) and 0.85 (95% CI 0.75-0.97), respectively. The relative 1-year ongoing pregnancy chance was highest for the centres no.10, 4 and 11 with HRs 1.33 (95% CI: 1.20-1.48), 1.22 (95%

Table I Patient characteristics* per IVF centre

Centre	Patients[a]	Age (years)			Duration of subfertility (years)			Pregnancy history		Diagnostic category / Cause of subfertility						
		< 30	30-34	≥ 35	< 3	3-6	≥ 6	Primary	Secondary	Tubal	ECI[b]	Male IVF	Male ICSI	Endom[c]	Horm[d]	Immun[e]
No.	No.	%			%			%		%						
1	125	15	31	54	43	43	14	62	38	28	22	9	27	2	9	3
2	284	19	34	47	43	43	14	61	39	11	16	6	59	5	1	2
3	267	18	53	29	46	45	9	71	29	16	22	58		4	0	0
4	613	20	48	32	59	34	7	72	28	12	30	14	26	5	10	3
5	296	24	44	32	46	43	11	64	36	19	21	22	19	4	13	2
6	65	25	29	46	51	40	9	69	31	11	31	49		3	6	0
7	557	24	47	29	45	46	10	69	31	17	22	18	24	5	9	4
8	511	23	45	32	53	41	6	66	34	20	12	23	28	5	6	6
9	564	19	48	34	45	48	8	57	43	16	18	15	28	10	9	3
10	860	16	41	43	37	52	12	63	37	20	29	21	22	2	4	3
11	786	17	40	43	35	48	18	59	41	25	13	11	38	8	3	1
Total	4928	20	42	38	46	44	11	65	35	18	22	47		5	6	3

[a] Patients at first cycle.
[b] Unexplained subfertility.
[c] Endometrioses.
[d] Hormonal disturbances.
[e] Immunologic or cervical subfertility.
*P < 0.001 (Chi squared test) for all characteristics.

Table II Centre success rates after 12 months of treatment, in HRs, relative to the average of all centres

Centre	A			B			C		
	Unadjusted			Random effects, unadjusted			Random effects, adjusted		
	HR	95% CI		HR	95% CI		HR	95% CI	
1	0.48	0.34	0.69	0.66	0.51	0.85	0.74	0.57	0.94
2	0.89	0.74	1.07	0.89	0.75	1.06	0.90	0.76	1.08
3	1.30	1.10	1.54	1.22	1.03	1.44	1.12	0.95	1.31
4	1.34	1.18	1.51	1.28	1.13	1.44	1.22	1.08	1.38
5	1.05	0.89	1.24	1.02	0.87	1.20	1.01	0.86	1.18
6	1.11	0.79	1.55	1.04	0.80	1.37	1.04	0.80	1.36
7	0.95	0.83	1.09	0.93	0.82	1.06	0.89	0.78	1.02
8	0.87	0.76	1.00	0.87	0.76	0.99	0.85	0.74	0.97
9	0.95	0.83	1.09	0.94	0.82	1.07	0.92	0.81	1.05
10	1.29	1.16	1.44	1.24	1.12	1.38	1.33	1.20	1.48
11	1.13	1.01	1.26	1.09	0.98	1.22	1.13	1.01	1.27

CI: 1.08-1.38) and 1.13 (CI: 1.01-1.27), respectively. With the adjustment for differences in female age, duration of subfertility, diagnostic category and primary versus secondary, 17% of the variation between centres was explained. The 1-year ongoing pregnancy chance of the centre with the lowest and the highest HRs were 36% and 55%.

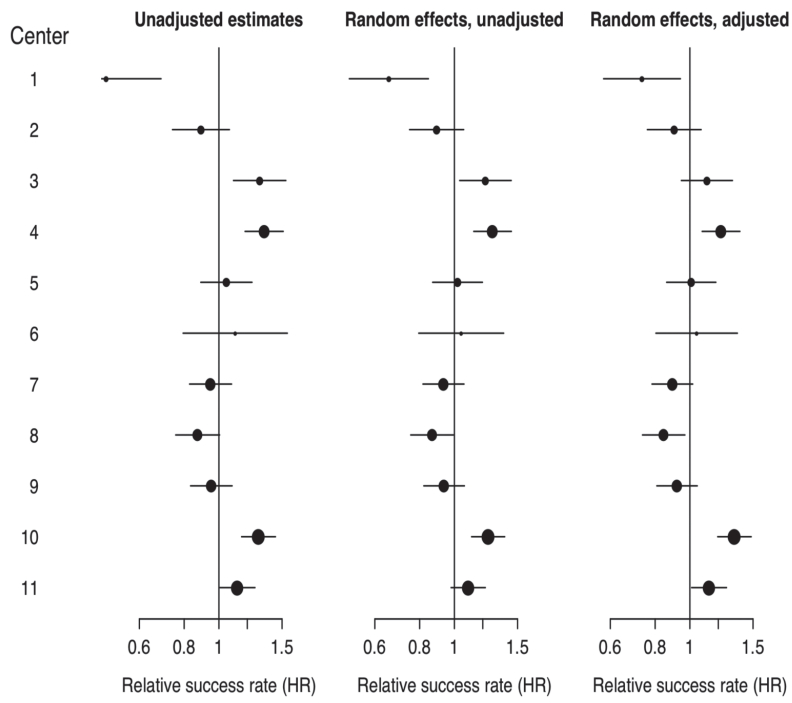
In Table III, we give a similar presentation of the ongoing pregnancy rates in odds ratios (ORs) per first IVF cycle to account for differences in time span between attempts for the different centres. Figure 2 is corresponding to the table. The estimates per centre after random effects and patient mix adjustment were comparably related to the average of all centres, as in the HRs of the 1-year ongoing pregnancy rates.

Figure 3 presents the relationship between the real size of the centres by the number of IVF cycles started in 2003, obtained from the public LIR data (www.lirinfo.nl), and the HRs of the relative 1-year ongoing pregnancy rates after adjustments. The slope of the line shows a positive association with centre size and pregnancy rates, although not significant p=0.34.

Discussion

Differences in 1-year ongoing pregnancy rates between IVF centres in the Netherlands exist, even after adjustment for sampling variation and patient mix. The estimated HRs for the 1-year ongoing pregnancy chance was 36% for the centre with the lowest estimate and 55% for the centre with the highest estimate.

Figure 1 The first graph gives the unadjusted ongoing pregnancy chance after 12 months of treatment, per centre. The second graph presents the estimates per centre adjusted for sampling variability. The third graph gives the estimates after adjustment for patient mix. The size of the spot corresponds with the size of the sample, but not with the actual size of the centre



The average ongoing pregnancy chance after the first cycle for all centres was 24% (Lintsen *et al.,* 2007). The ongoing pregnancy rate per cycle after adjustment for patient mix was 12% in the centre with the lowest odds ratio (0.45), compared to 28% for the centre with the highest odds ratio (1.25) (data for patient mix adjustment only are not shown). Substantial differences between clinics were also seen in the study of Marshal and Spiegelhalter (1998). The per cycle "live birth" rate after adjustment for patient mix ranged from 5% to 24% per IVF clinic in the UK. The absolute differences between success rates of clinics in the UK and between centres in the Netherlands seem to be comparable. On the other hand there is an apparent relative difference between the success rates of clinics in both countries. Almost a

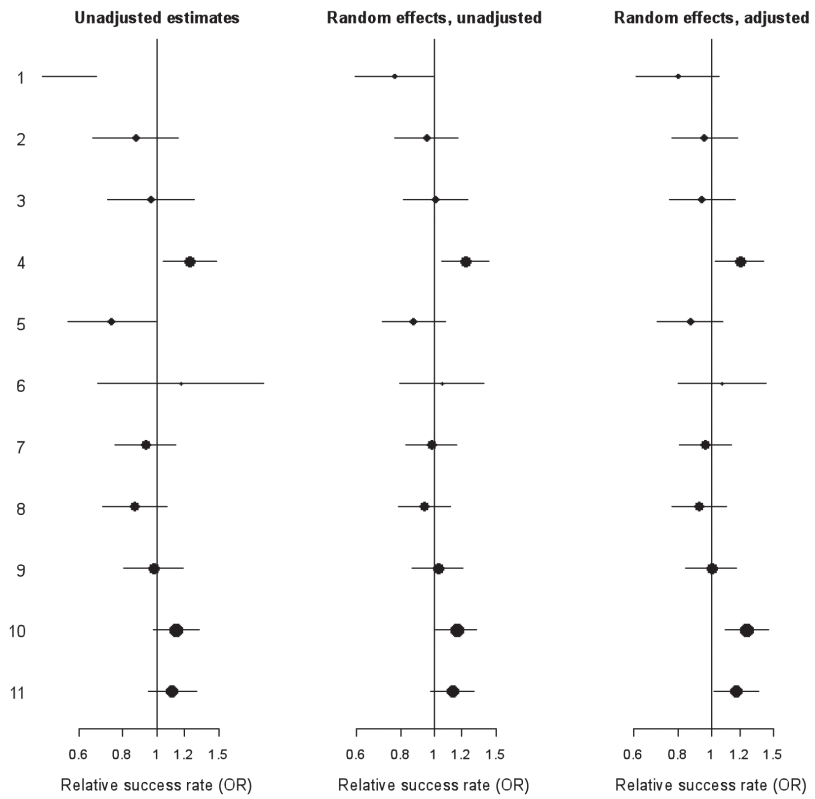
Table III First IVF cycle success rates, in ORs, relative to the average of all centres

Centre	A			B			C		
	Unadjusted			Random effects, unadjusted			Random effects, adjusted		
	OR	95% CI		OR	95% CI		OR	95% CI	
1	0.39	0.22	0.67	0.77	0.60	1.00	0.80	0.61	1.05
2	0.87	0.66	1.15	0.95	0.77	1.17	0.95	0.77	1.18
3	0.96	0.73	1.27	1.01	0.82	1.24	0.94	0.76	1.16
4	1.24	1.04	1.48	1.22	1.05	1.43	1.20	1.02	1.40
5	0.74	0.56	0.99	0.87	0.71	1.08	0.87	0.70	1.08
6	1.17	0.68	2.01	1.05	0.80	1.38	1.07	0.80	1.42
7	0.93	0.76	1.13	0.98	0.83	1.16	0.96	0.81	1.14
8	0.87	0.70	1.07	0.94	0.79	1.12	0.92	0.77	1.10
9	0.98	0.81	1.19	1.02	0.87	1.20	0.99	0.84	1.18
10	1.13	0.98	1.32	1.15	1.01	1.32	1.25	1.09	1.44
11	1.11	0.94	1.30	1.13	0.98	1.30	1.17	1.02	1.36

factor 5 difference for the "worst" compared to the "best" performing clinic in the U.K., compared to a factor 2.3 difference for the two extreme centres in the Netherlands. Data collection took part with a time difference of 10 years between the two studies and IVF outcome has improved during the past years. Further, non-privatized centres and adherence to a national guideline will lead to uniformity between centres and more or less equality in chance per couples treated. The IVF guideline intents to hold back couples with still a high chance to conceive spontaneously by determining a minimum for the duration of subfertility and discourages couples with a very low chance to conceive by maintaining a maximum women's age for treatment. We examined the adherence to one of the recommendations in the guideline IVF: "IVF should be withheld for couples with unexplained subfertility when the duration of subfertility is less than 3 years and the woman's age is under 36" (Table IV). When comparing only centres with a reasonable number of participants in this category, we conclude that the adherence to the guideline was low for centre no. 4, and no. 7. This "early" reference for IVF may increase the overall pregnancy rate. The variation in adherence to the guideline-based indicators between Dutch IVF clinics has been studied by Mourad *et al.* (2008); they found the median adherence to the guideline IVF was high: 86%. In case of unexplained subfertility the adherence was fairly high 79% (range 67-92%).

Large differences in size of the centres adds to an important difficulty in comparison between centres, but in the Netherlands there are no real small IVF centres. The number of treatments in

Figure 2 The first graph gives the unadjusted ongoing pregnancy chance after the first cycle, per centre. The second graph presents the estimates per cycle after adjustment for sampling variability. The third graph gives the estimates after adjustment for patient mix. The size of the spot corresponds with the size of the sample, but not with the actual size of the centre

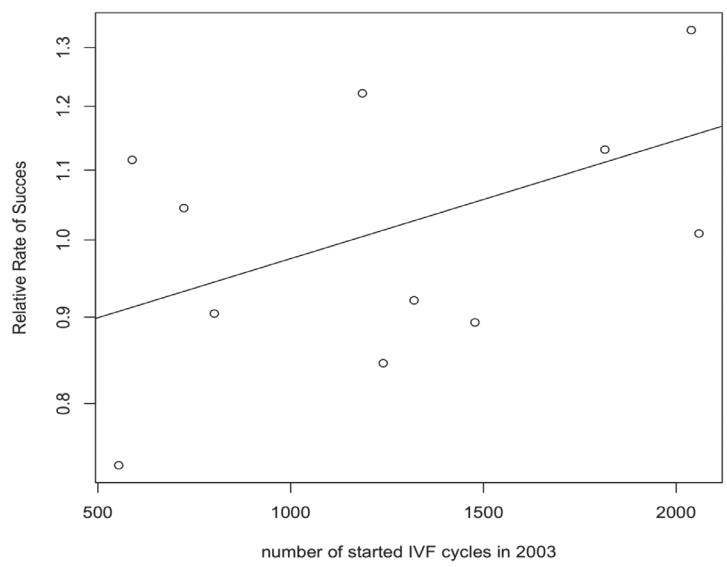


2003, of the centres included in the study ranged between 589 and 2059 cycles per year (mean 1314; www.lirinfo.nl), In comparison, in British IVF centres, the number of cycles ranged between 68 and 1453 (mean 469), cycles per year (Marshal and Spiegelhalter, 1998) and between 10 and 3054 cycles in Spanish IVF centres. (Castilla et al., 2008). The fact that all Dutch centres were equally big in size and for that reason, dexterity does not play a role, might explain why we did not find a relationship between centre size and success rates in Figure 3.

Table IV Duration of subfertility for women with unexplained subfertility aged ≤ 35 at the start of IVF, per centre

Centre	Duration of subfertility		
	< 3 years (n)	≥ 3 years(n)	≥ 3 years (%)
1	3	5	63
2	1	9	90
3	7	35	83
4	50	60	55
5	6	31	84
6	3	6	67
7	28	51	65
8	6	27	82
9	11	47	81
10	25	102	80
11	8	48	86
Total	148	421	74

Figure 3 The relationship between the actual size of the centres by the number of IVF cycles started in 2003 and the estimates of the pregnancy rates per centre after adjustment for random effects (p=0.34)



Nevertheless, despite the guideline, size, and only state-funded IVF centres, the confidence intervals around the relative 1-year ongoing pregnancy rates are wide, expressing that there is still a great uncertainty about the true estimates. After adjustment for patient mix, the relative rates per centre did not change substantially, indicating a minor role for patient mix as registered in the IVF databases on the outcome per centre. On the other hand, the patient characteristics included in the prognostic index may not adjust for all patient related factors present. Sharif and Afnan (2003) suggested that comparison of clinics on a valid basis could be solved by comparing the IVF outcome of a standard patient group. This was rebutted by Johnson *et al.* (2007). They found that in the same clinic, two standardized patient groups, who were selected based on the area of residence, had a significant difference in outcome. Most known variables to influence IVF outcome were adjusted for, but patients differed in ethnicity and lifestyle, and also cause of subfertility.
To be more complete, at least lifestyle should be included in the registration. For this study, a centre that excluded overweight women and/or smokers could for this reason have a higher 1-year ongoing pregnancy chance compared to the others.

The random effects approach relies on the assumption that the centres in our study form a sample of the 'population' of centres, at least in theory. More important, the relative hazards in this population are assumed to follow a normal distribution, after logarithmic transformation. The fact that the per-centre estimates are shrunk towards the mean by the random effects model for most of the centres is a direct consequence of this assumption: it assumes that the centres vary around a central mean. If in reality there are two types of clinics, one type with on average low success rates, the other one with relatively high success rates, a distribution with two peaks would have been more appropriate. An example would be a country with a dual healthcare system, partly state-funded and partly commercial. In the Netherlands, all IVF centres are non-commercial. The clinics operate in a level playing field making the assumption of variation around a central mean plausible. With this statistical computation used, differences in the 1-year ongoing pregnancy rates between centres are presented in a way that the margin of uncertainty is adjusted for sampling variability and patient mix. The mutual position of the centres did not change after adjustment, indicating that the influences of patient mix are not as strong as often suggested. Further, the variation without adjustment was only slightly larger than the variation with adjustment, and a modest 17% of the differences between centres can be explained by patient mix.
Several validation studies have concluded that differences in pregnancy outcome rate between clinics have important limitations for the reproducibility of prediction models (Stolwijk *et al.,* 1998, Smeek *et al.*, 2000, Hunault *et al.,* 2007). By chance alone, pregnancy rates may vary from year to year and natural variation causes fluctuations in results (Kremer *et al.*, 2008).

In this paper we intentionally avoided to present performance data for centres, as league tables and control charts. These ranking methods are critically discussed by, Winston (1998), Adab *et al.* (2002), Marshall and Rouse (2004), Lemmers *et al.* (2007) and Castilla *et al* (2008). Data used for comparison may never contain all relevant factors, but the impact of any kind of ranking on health providers, consumers and media is high. Instead, we aimed to quantify the absolute difference in the 1-year ongoing pregnancy rates per centre taking account of sampling variability and patient mix. However, important outcome measures of IVF treatment as multiple pregnancies, pregnancies from cryo-preserved embryos, risks of ovarian hyper-stimulation syndrome and psychological burden after unsuccessful IVF is lacking. According to the LIR registration of 2003, on average the centres had a 19% chance of ongoing twin pregnancy (range 10-29%), and 9% of all ongoing pregnancies were derived from frozen and thawed embryos (range 1,5-25%). Another limitation of this study is that not all patient characteristics could be adjusted for e.g. ethnicity, socio-economic variations and lifestyle.

With this study we can conclude that there are remaining differences in pregnancy rates for the IVF centres in the Netherlands, with the extremes of the 1-year ongoing pregnancy chance laying between 36% and 55%. To find the explanations for the differences between IVF centres, we recommend further investigation of factors that could influence the pregnancy chance, e.g. lifestyle, but also to look beyond patient related factors as e.g. differences between IVF laboratories.

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3

Chapter | 4

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

4

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Abstract

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 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-month 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.

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 months 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, intra uterine 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 that 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 asses 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 gynecologist 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 esthablished. 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 of 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 least12 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 mal 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.

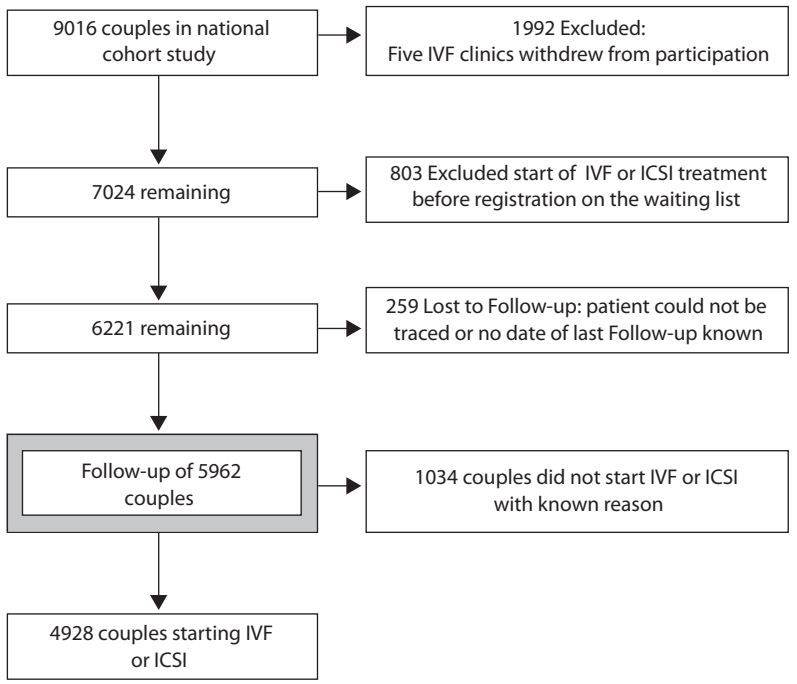
Multivariable Cox regression was used to analyse the impact of prognostic factors on the chance of treatment-free pregnancy. Factors considered were the age of the woman, the duration of infertility, the diagnostic category mentioned as the indication for IVF and

whether infertility of the couple was primary or secondary. The internal validity of the resulting model, i.e. how well does the model predict the 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 form a low chance couple (Harrell *et al.,* 1996).
The outcome of a pregnancy (whether it was ongoing or not) was not in all 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 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.,* 2005). For 5962 patients, the follow-up could be established, and they form the basis of analysis (Figure 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.

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



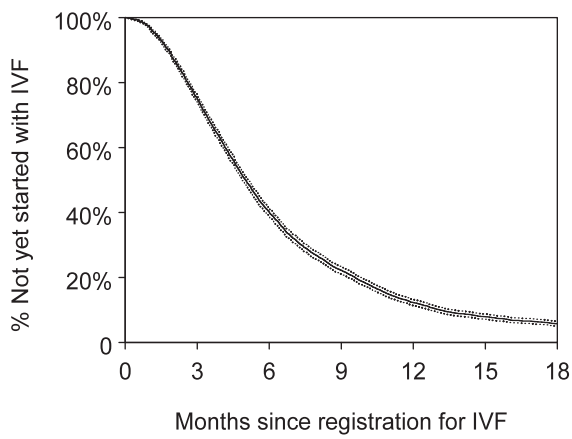
The time on the waiting list before starting IVF is shown in Figure 2. The total treatment-free follow-up was 33,813 months (median 4.6 months), with a median duration of follow-up of 2.5 months for the pregnant patients, 4.5 months for the patients that started IVF and 6.2 months for the patient who 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 Figure 3.

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

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



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

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

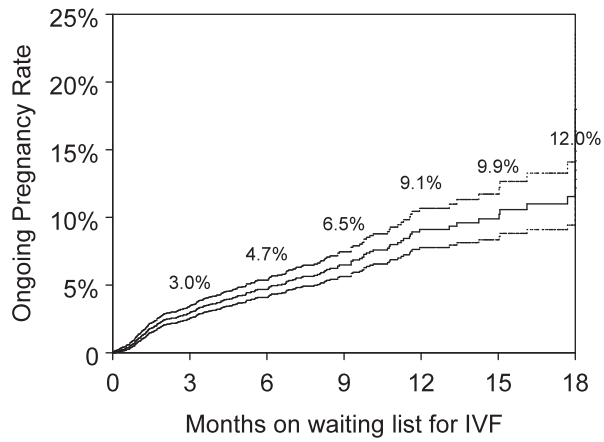


Figure 4 Cumulative chance of an ongoing treatment-free pregnancy, against time since registration on the waiting list for IVF or ICSI, separately for diagnostic categories. Kaplan-Meier estimates, censoring for start of treatment and for termination of the active childwish

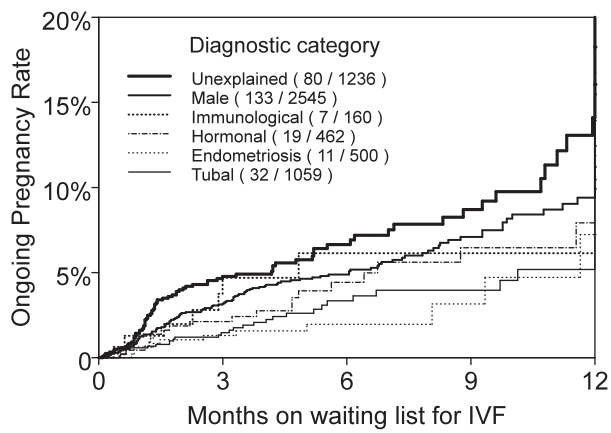


Table II HR for ongoing pregnancy without treatment of 5962 patients on the waiting list for IVF

	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 vs. secondary infertility	0.71	0.56- 0.90

* Reference group

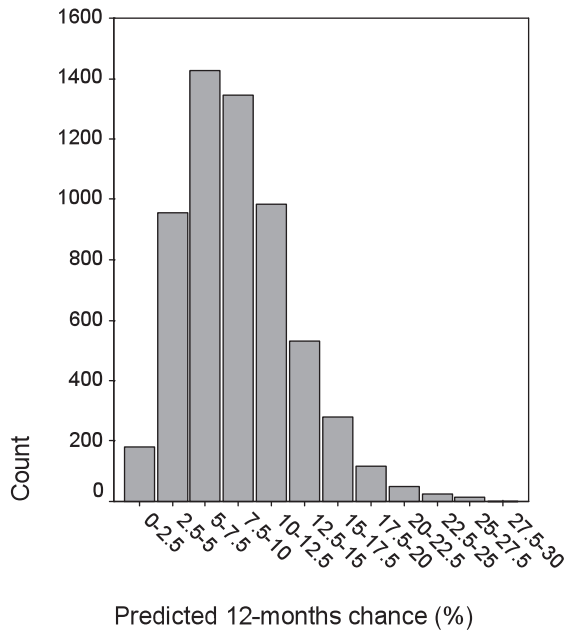
additional year) and for primary compared to secondary infertility (HR = 0.71, a 29% relative reduction). The 12 months chances of pregnancy without treatment predicted by the Cox regression model are shown in Figure 5. Predictions range from 0% to about 25%, with 8.3% of patients having a predicted 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 form 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).

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



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 to 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.fertlitetsselskab.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) compromising 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.

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 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 Follicle Stimulating Hormone (FSH) and the antral follicle count (AFC) 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 prediction model with even less discriminative power (Hunaults *et al.,* 2004).

The main research question of this study was: what are the pregnancy chances of couples that 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.

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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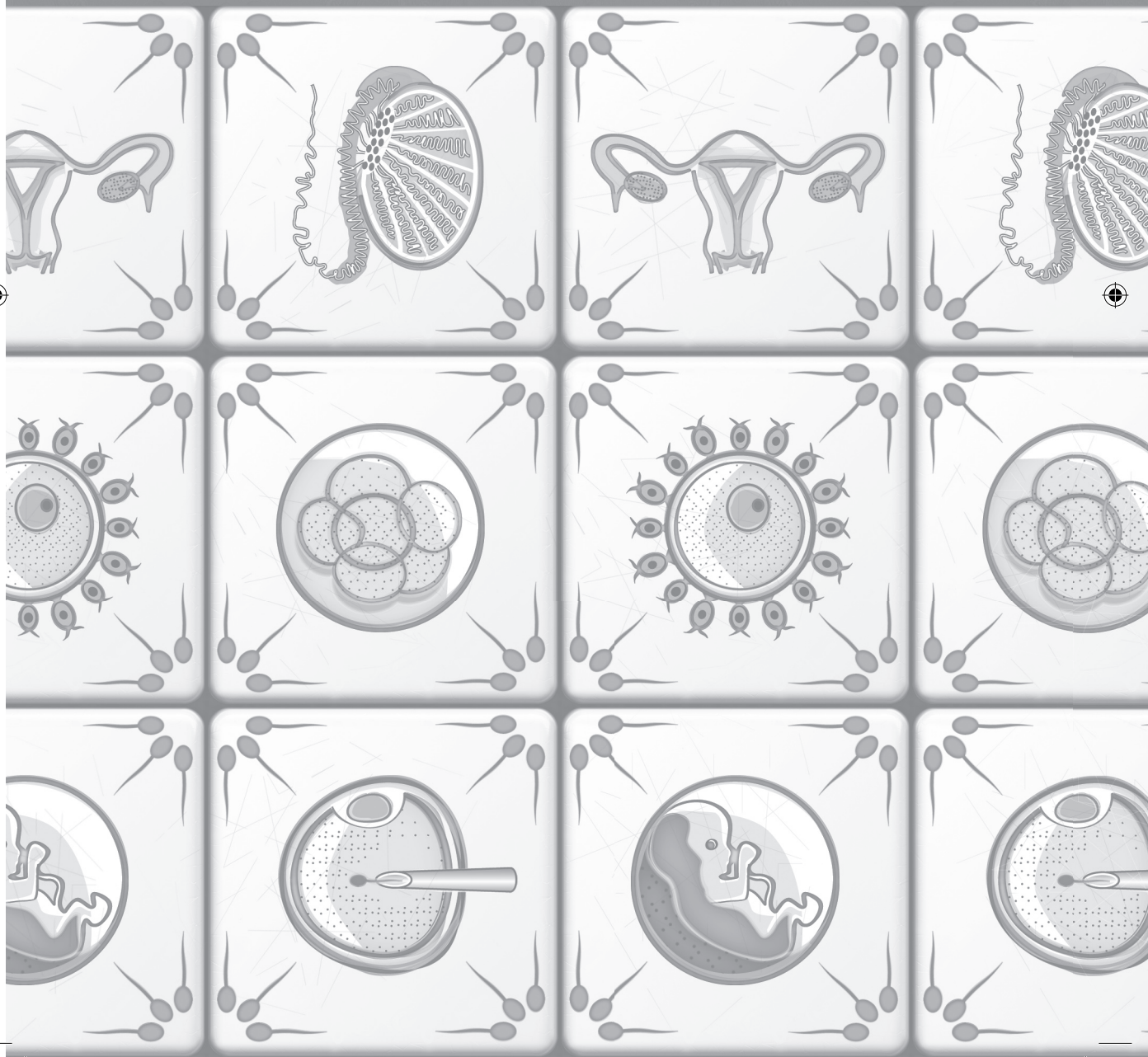
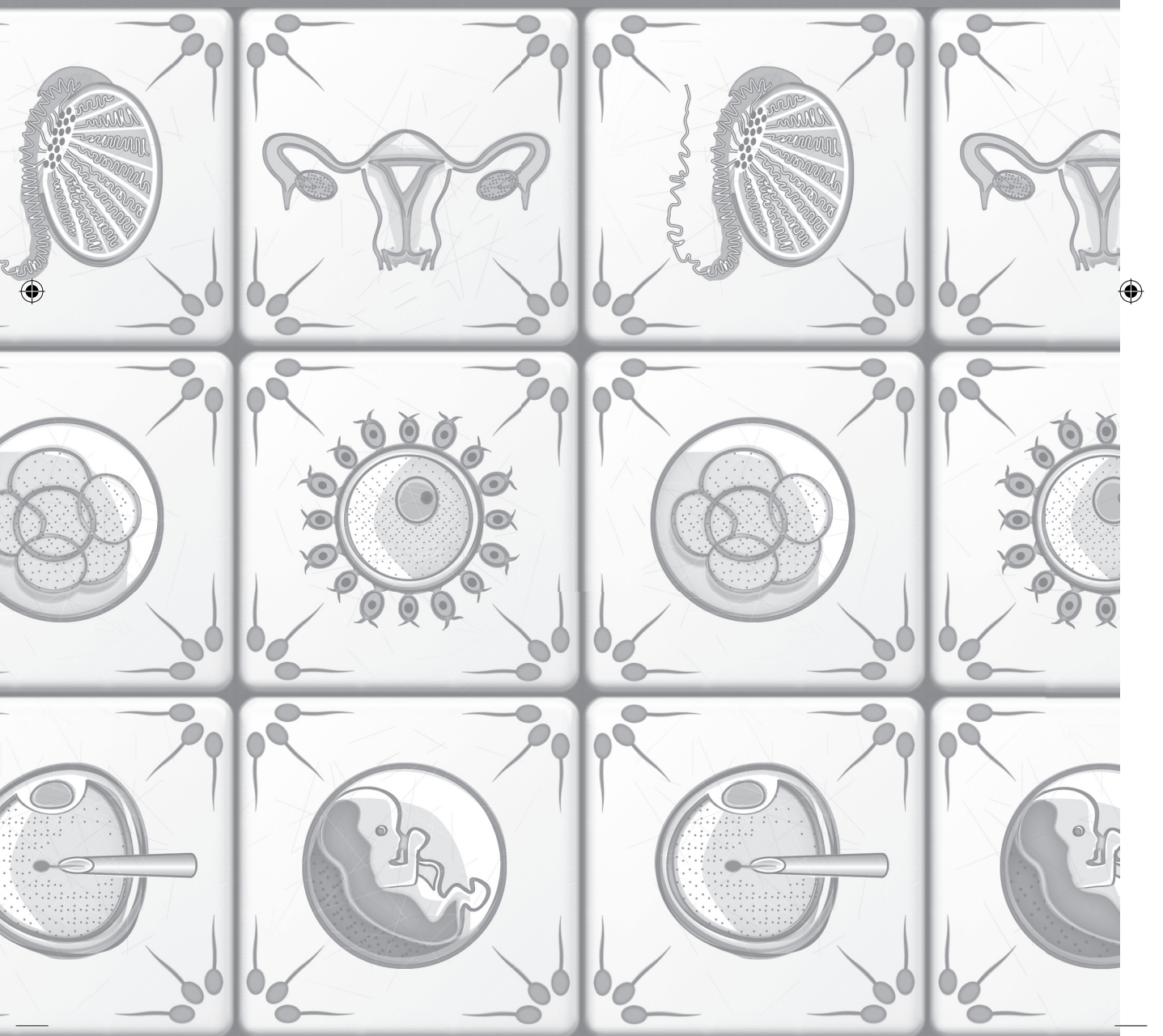


Part | II

Lifestyle and Psychological factors



Chapter | 5

Effects of subfertility cause, smoking and body weight on the success rate of IVF

5

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Abstract

Background: We investigated the separate and combined effects of smoking and body-mass index (BMI) on the success rate of IVF for couples with different causes of subfertility.

Methods: The success rate of IVF was examined in 8457 women. Detailed information on reproduction and lifestyle factors was combined with medical record data on IVF treatment. All IVF clinics in the Netherlands participated in this study. The main outcome measures were live birth rate per first cycle of IVF differentiated for the major predictive factors.

Results: For male subfertility the delivery rate per cycle was significantly lower than for unexplained subfertility, OR of 0.70 (95% CI: 0.57- 0.86); for tubal pathology, the delivery rate was slightly lower, OR = 0.86 (95% CI: 0.70 – 1.01). Smoking was associated with a significantly lower delivery rate, OR = 0.72 (95% CI: 0.61 - 0.84) and a significantly higher abortion rate compared to non-smoking, delivery rates of 21.4% and 16.4%, respectively (p=0.02). Women with a BMI of ≥ 27 kg/m^2 had a significantly lower delivery rate, with an OR of 0.67 (95% CI: 0.48 – 0.94), compared with normal weight women (BMI ≥ 20 and < 27 kg/m^2).

Conclusions: Both smoking and overweight unfavourably affect the live birth rate after IVF. The devastating impact of smoking on the live birth rate in IVF treatment is comparable with an increase in female age of > 10 years from age 20 to 30 years. Subfertile couples may improve the outcome of IVF treatment by life style changes.

Introduction

The improving success rates of IVF, initially developed as a technique to assist reproduction in women with bilateral tubal obstruction (Steptoe and Edwards, 1978), have extended its use to other subfertility diagnoses. For women with severe bilateral tubal occlusion evidence for the effectiveness of IVF has been available for years (Corabian and Hailey, 1999). Recently a randomised controlled trial (RCT), although small, suggested the efficacy of IVF for subfertility causes other than tubal pathology (Hughes *et al*., 2004). Other studies on the success rate of IVF by cause of subfertility have shown inconsistent results (Alsalili *et al*., 1995; Tan *et al*., 1996). However, in the largest study on IVF effectiveness (Templeton *et al*., 1996), carried out in the UK between 1991 and 1994 and including 36,961 cycles, no significant differences were observed in live birth rate comparing tubal pathology, endometriosis, unexplained subfertility and cervical and uterine subfertility. The prognostic model developed by Templeton *et al*. did not give additional predictive information for the majority of IVF patients in the Netherlands in the study by Smeenk *et al*. (2000). Life style factors were not included in these studies.

The main goal of the present analyses was to explore possible predictive factors such as duration of subfertility, and female age, for subfertile couples with different causes of subfertility. As there is evidence of an overall detrimental effect of female smoking on natural and assisted fecundity in the literature (Hughes and Brennan *et al*., 1996; Feightinger *et al*., 1997; Augood *et al*., 1998; Hassan and Killick, 2004) and indication for an unfavourable effect of extremes of BMI on the outcome of fertility treatment (Norman and Clark, 1998; Wang *et al*., 2000; Wang *et al*., 2002; Nichols *et al*., 2003), we also studied smoking and BMI as possible prognostic factors. Like the Templeton model we distinguished the major causes of subfertility, and added male subfertility and life style factors. We executed this study with data from a large Dutch nationwide retrospective cohort study (the so called "OMEGA study") including 19,840 women who underwent IVF treatment between 1983 and 1995.

Materials and Methods

Patients

The study population, study procedures and data collection methods have been described elsewhere (Klip *et al*., 2001, 2003; de Boer *et al*., 2003). In short, the OMEGA-study, initiated in 1995 to examine the late effects of hormone stimulation in IVF treated women, comprised 19,840 women treated with IVF in a nationwide cohort study. Women with subfertility of ≥ 1 year duration were included if they had completed at least one IVF treatment cycle between January 1, 1983, the start of IVF treatment in the Netherlands and January 1, 1995. A 23-page

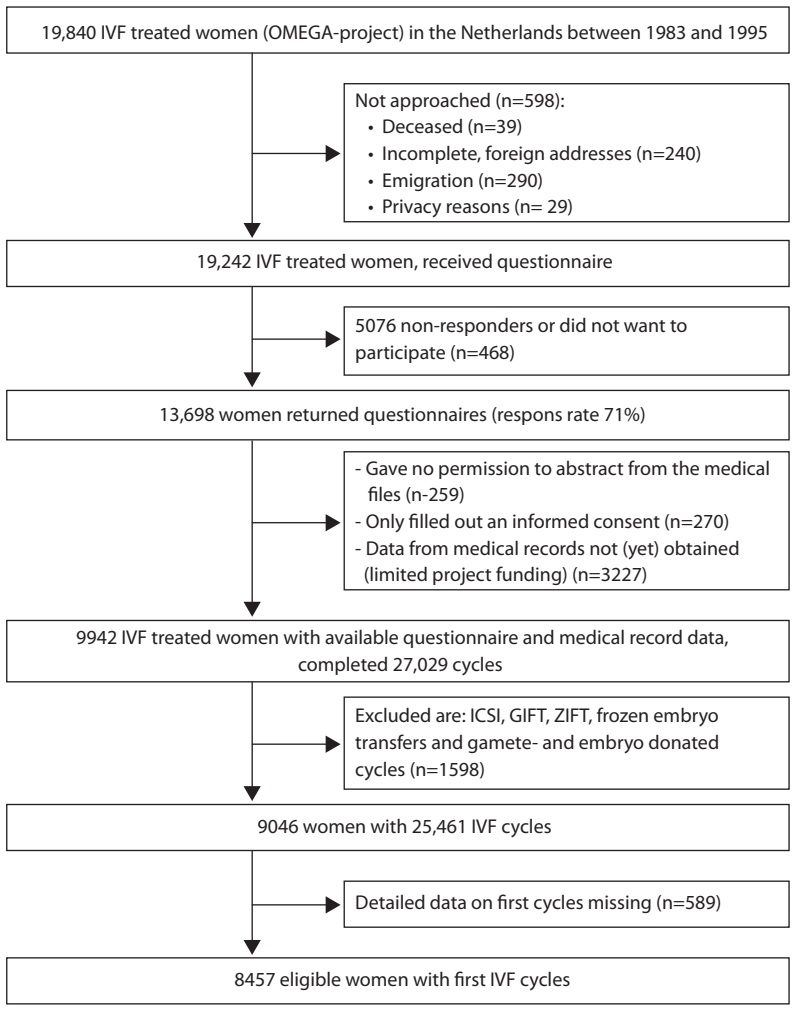
questionnaire was sent to 19,242 women between January 1997 and January 2000 to obtain information on gynaecological disorders before and after subfertility treatment, reproductive risk factors for hormone-related cancers and several other lifestyle factors. Figure 1 gives a graphical presentation of the study population. As there was no national registry of IVF treatments, data from both the patient records and pregnancy follow-up were collected by trained research assistants, who abstracted data from the medical files on gynaecological history, subfertility diagnosis, fertility hormones used prior to IVF treatment, and detailed information about each subsequent IVF treatment, the number of retrieved oocytes, occurrence of complications and whether or not the treatment resulted in a pregnancy. Additional information on pregnancy outcome, reproductive and lifestyle factors were obtained through the mailed questionnaire.
For the present analyses, all ICSI attempts were excluded because of the small number. Unstimulated cycles, other IVF related treatments such as zygote intra fallopian transfer (ZIFT), gamete intra fallopian transfer (GIFT), gamete and embryo donation and frozen embryo transfers were also excluded from the study (in total 1568 cycles).

In the Netherlands three IVF cycles were covered by health cost insurances in the period under study, leading to a low drop out rate in the first three cycles. Eighty-seven percent of the women completed at least three cycles, or became pregnant in the first two cycles. As continuation of IVF depends on predictors of success observed in the first cycle, such as number of oocytes, fertilization rate and embryo morphology (Stolwijk *et al*., 1996) we restricted all analyses to the first attempt. Leaving 8457 first cycles for analysis.

Definition of variables

Subfertility diagnosis was based on medical record information and divided into 4 categories: tubal pathology, male subfertility, unexplained subfertility and other known subfertility causes, mainly women with polycystic ovary syndrome (PCOS) or endometriosis. Each woman was only categorized once, the one assumed to contribute most to the subfertility. For 831 first cycles there was no cause of subfertility known and were therefore not analysed in detail. Duration of subfertility was determined by the period between the start of the involuntary childlessness, as reported by the woman, and the date of first IVF attempt. Primary subfertility was defined as having no pregnancy before the IVF treatment. Education level was divided into low (those without completed vocational training), middle (with vocational training) and high (with high vocational training or academic degrees). Women were defined as smokers when they smoked more than one cigarette a day for ≥1 year at the time of the first oocyte retrieval. Underweight was defined as having a BMI <20 kg/m^2, normal weight as a BMI of 20-27 kg/m^2 and overweight as a BMI ≥ 27 kg /m^2, as there were not enough women with a BMI ≥ 30 kg/m^2 for analysis. The BMI was calculated with the women's weight at the

Figure 1 Description of the recruitment of eligible women and cycles. GIFT= gamete intra fallopian transfer; ZIFT= zygote intra-fallopian transfer



time of first visit to the gynaecologist for her fertility problem. The woman's age at the IVF attempt was computed by subtracting the date of birth from the IVF attempt date. IVF attempts obtained from the medical records were linked with livebirths as reported by the women on the questionnaire. Conception dates were calculated by subtracting the reported

duration of pregnancy from the delivery date, as reported by the women. If an IVF attempt had started within 4 weeks of the estimated conception date, the pregnancy was considered to be the result of the IVF attempt, unless the medical record stated that a spontaneous pregnancy followed the IVF attempt. The implantation rate was defined as the number of live born children per embryo transferred. The live birth rate was the delivery rate with at least one live born child per cycle. Total fertilization failure (TFF) was defined when none of the oocytes were fertilized after IVF. An abortion was defined as a pregnancy loss between 6 and16 weeks of amenorrhoea. The following complications were registered: ovarian hyperstimulation syndrome (OHSS) leading to hospitalization, other medical problems resulting in admission and ectopic pregnancies.

Statistical analyses

The statistical program SAS: The SAS system for windows 8.2, SAS Institute Inc. Cary NC, USA, was used for statistical analyses. Univariate frequencies and means were calculated to describe the women and their first IVF cycles. The results are given in Tables I and II. All analyses were done first on all women, including those with unknown cause of subfertility, and then by cause of subfertility.

Contingency tables were used to calculate live birth rates per cycle, live birth rate per oocyte retrieval and live birth rate per embryo transfer as well as the implantation rate for categories according to the cause of subfertility, age, smoking, period of IVF and BMI (Tables III and IV). This figure was then averaged across cycles.

Multivariate logistic regression was done to study the independent and combined effects of potential determinants on the live birth rate. We included cause of subfertility, smoking, BMI (continuous and in three categories) and period of IVF in the model, together with factors that have previously been reported in the literature to predict the success rate of IVF. These factors were: primary versus secondary subfertility, age at treatment (continuous and in two categories) and duration of subfertility. We corrected for period of IVF by adding a factor indicating whether the IVF was before or after January 1, 1990. In univariate analyses, we found higher pregnancy rates after 1990 than before that date; however, differences in live birth rates over time were small. The results for the other variables included in the model did not change according to whether we included age and BMI as categorical or continuous variables. We included the results for the categorical variables in Table V and added the estimates for the continuous variables per unit change to the text. The resulting regression estimates were transformed to present odds ratios (OR) for those in a category as compared with the reference category, with all other factors equal.

Table I Characteristics of women in the OMEGA cohort at first IVF cycle

	All women in first cycle[a]	Tubal pathology	Male subfertility	Un-explained subfertility	Other known subfertility causes[b]
No. of first cycles	8457	3008 (35.6)	2179 (25.8)	1828 (21.6)	611 (7.2)
Age (years)					
Average (SD)	32.8 (3.9)	32.8 (4.0)	32.4 (3·9)	33.3 (3.7)	32.5 (3.9)
20-24	187 (2.2)	80 (2.7)	48 (2.2)	22 (1.2)	19 (3.1)
25-29	1833 (21.7)	653 (21.7)	553 (25.4)	326 (17.8)	135 (22.1)
30-34	3915 (46.3)	1361 (45.3)	1014 (46.5)	862 (47.2)	290 (47.5)
35-39	2262 (26.7)	821 (27.3)	520 (23.9)	556 (30.4)	151 (24.7)
≥40	235 (2.8)	86 (2.9)	40 (1.8)	59 (3.2)	4 (2.3)
Unknown	25 (0.3)	7 (0.2)	4 (0.2)	3 (0.2)	2 (0.3)
Duration of subfertility (years)					
Mean (SD)	5.35 (3.0)	5.11 (3.3)	5.34 (2.9)	5.60 (2.7)	5.83 (3.2)
Median (IQR)	4.65 (3.3)	4.33 (3.7)	4.64 (3.1)	4.89 (2.8)	5.08 (3.6)
Unknown	1286 (15.2)	434 (14.4)	245 (11.2)	140 (7.7)	50 (8.2)
Subfertility					
Primary	4009 (47.4)	1090 (36.2)	1246 (57.2)	1044 (57.1)	366 (59.9)
Secondary	1944 (23.0)	974 (32.4)	305 (14.0)	460 (25.2)	90 (14.7)
Unknown	2504 (29.6)	944 (31.4)	628 (28.8)	324 (17.7)	155 (25.4)
Level of education[c]					
Low	2323 (27.5)	862 (28.7)	567 (26.0)	478 (26.1)	194 (31.8)
Middle	4085 (48.3)	1421 (47.2)	1095 (50.3)	888 (48.6)	255 (41.7)
High	1865 (22.1)	651 (21.6)	475 (21.8)	423 (23.1)	152 (24.9)
Unknown	184 (2.2)	74 (2.5)	42 (1.9)	39 (2.1)	10 (1.6)
Smoking at 1st IVF					
Yes	3617 (42.8)	1536 (51.1)	841 (38.6)	673 (36.8)	229 (37.5)
No	4706 (55.6)	1423 (47.3)	1306 (59.9)	1127(61.7)	371(60.7)
Unknown	134 (1.6)	49 (1.6)	32 (1.5)	28 (1.5)	11 (1.8)
BMI (kg/m^2) at 1st IVF					
Average (SD)	22.27 (3.3)	22.36 (3.3)	22.25 (3.1)	22.04 (3.1)	22.46 (3.6)
<20	1752 (20.7)	607 (20.2)	433 (19.9)	409 (22.4)	134 (21.9)
20-25	5132 (60.7)	1818 (60.4)	1357 (62.3)	1127 (61.7)	351 (57.4)
25-27	602 (7.1)	228 (7.6)	144 (6.6)	110 (6.0)	52 (8.5)
>27	619 (7.3)	231 (7.7)	153 (7.0)	117 (6.4)	46 (7.5)
Unknown	352 (4.2)	124 (4.1)	92 (4.2)	65 (3.6)	28 (4.6)

Values in parentheses are percentages unless otherwise specified. [a] Including those with unknown subfertility cause. [b] Including polycystic ovary syndrome 16.5%, other ovarian problems 28.8%, endometriosis 34.4%, other causes 21.3%. [c] Low= not completed vocational training, middle = with vocational training, high = high vocational training and academic training. SD = standard deviation. IQR=interquartile range.

Table II Characteristics and various outcome measures of first IVF cycles of women in the OMEGA cohort

	All subfertility	Tubal pathology	Male subfertility	Un-explained subfertility	Other known causes
No. of cycles (% of all first cycles)	8457	3008 (35.6)	2179 (25.8)	1828 (21.6)	611 (7.2)
With oocyte retrievals	7529 (89.0)	2636 (87.6)	1995 (91.6)	1644 (89.9)	530 (86.7)
Median no. of oocytes (IQR) (25-75)	8 (5–12)	8 (4–12)	8 (5–13)	8 (5–12)	8 (5–13)
With embryo transfers	6286 (74.3)	2388 (79.4)	1389 (63.7)	1437 (78.6)	469 (76.8)
Median no. of embryos (IQR) (25-75)	2 (1–3)	3 (2–3)	2 (0–3)	2 (2–3)	2 (2–3)
No. of pregnancies [a]	1664 (19.7)	580 (19·3)	369 (16.9)	418 (22.9)	140 (22.9)
No. of abortions [bc]	313 (18.8)	118 (20.3)	57 (15.5)	84 (20.1)	30 (21.4)
Deliveries [a]	1282 (15.2)	439 (14.6)	296 (13.6)	326 (17.8)	103 (17.0)
No. of singletons [d]	915 (71.4)	312 (71.1)	205 (69.3)	228 (69.9)	79 (76.7)
No. of twins [d]	310 (24.2)	101 (23.0)	81 (27.4)	84 (25.8)	21 (20.4)
No. of triplets or more [d]	57 (4.4)	26 (5.9)	10 (3.4)	14 (4.3)	3 (2.9)
Complications					
TFF	1164 (13.8)	221 (7.3)	590 (27.1)	194 (10.6)	57 (9.3)
OHSS	206 (2.4)	58 (1.9)	58 (2.7)	49 (2.7)	25 (4.1)
Other	154 (1.8)	77 (2.6)	24 (1.1)	33 (1.8)	15 (2.5)
Ectopic pregnancies [c]	56 (3.4)	35 (6.0)	7 (1.9)	8 (1.9)	3 (2.1)

Values in parentheses are percentages unless otherwise specified.

[a] Percentage of cycle.

[b] Between 6-16 weeks of pregnancy.

[c] Percentage of pregnancies.

[d] Percentage of deliveries.

IQR = interquartile range; TFF= total fertilization failure; OHSS=ovarian hyperstimulation syndrome.

Table III Comparison of live birth rates and implantation rates, per diagnostic category, according to age

			Live birth rate per first cycle [a]						Implantation rate (%) [b]
			per cycle		per oocyte retrieval		per embryo transfer		
	Age (Years)	No. of deliveries	n	%	n	%	n	%	
Tubal pathology		439	3007	14.6	2635	16.7	2387	18.4	9.3
Male subfertility		296	2178	13.6	1994	14.8	1388	21.3	11.8
Unexplained subfertility		326	1827	17.8	1643	19.8	1436	22.7	12.2
Tubal pathology	20-24	21	80	26.3	75	28.0	70	30.0	16.1
	25-29	100	653	15.3	578	17.3	522	19.2	10.6
	30-34	208	1360	15.3	1195	17.4	1089	19.1	9.7
	35-39	108	821	13.2	709	15.2	645	16.7	7.4
	40-44	2	85	2.4	71	2.8	55	3.6	1.5
Male subfertility	20-24	10	48	20.8	46	21.7	31	32.3	18.3
	25-29	79	552	14.3	518	15.3	368	21.5	13.1
	30-34	141	1014	13.9	944	14.9	646	21.8	11.9
	35-39	62	520	11.9	446	13.9	314	19.8	9.6
	40-44	4	40	10.0	37	10.8	27	14.8	5.9
Unexplained subfertility	20-24	4	22	18.2	21	19.1	17	23.5	13.7
	25-29	68	326	20.9	294	23.1	255	26.7	14.5
	30-34	165	861	19.2	779	21.2	684	24.1	13.5
	35-39	85	556	15.3	495	17.2	433	19.6	9.5
	40-44	4	58	6.9	51	7.8	45	8.9	4.8

[a] Delivery rate with at least one live born. [b] Number of live born children per embryo transferred.

Table IV Comparison of live birth rates and implantation rates per diagnostic category, stratified by smoking, and body mass index (BMI)

				Live birth rate per first cycle [a]						Implantation rate (%) [b]
				per cycle		per oocyte retrieval		per embryo transfer		
	Smoking	BMI (kg/m²)	No. of deliveries	n	%	n	%	n	%	
Tubal pathology	Yes		208	1536	13.5	1330	15.6	1199	17.4	8.4
	No		228	1422	16.0	1264	18.0	1149	19.8	10.3
Male subfertility	Yes		98	840	11.7	762	12.9	534	18.4	10.1
	No		191	1306	14.6	1203	15.9	831	23.0	12.6
Unexplained subfertility	Yes		90	673	13.4	592	15.2	520	17.3	9.1
	No		233	1126	20.7	1026	22.7	897	26.0	14.1
Tubal pathology		< 20	98	607	16.1	546	18.0	494	19.8	10.0
		20-25	264	1817	14.5	1604	16.5	1461	18.1	9.2
		25-27	33	228	14.5	195	16.9	170	19.4	8.4
		≥ 27	29	231	12.6	191	15.2	171	17.0	9.2
Male subfertility		< 20	59	433	13.6	399	14.8	282	20.9	11.6
		20-25	191	1356	14.1	1244	15.4	856	22.3	12.1
		25-27	20	144	13.9	134	14.9	100	20.0	11.4
		≥ 27	20	153	13.1	135	14.8	92	21.7	13.2
Unexplained subfertility		<20	72	408	17.7	369	19.5	323	22.3	11.4
		20-25	207	1127	18.4	1017	20.4	899	23.0	12.4
		25-27	23	110	20.9	94	24.5	80	28.8	17.1
		≥ 27	16	117	13.7	103	15.5	86	18.6	11.5

[a] Delivery rate with at least one live born. [b] Number of live born children per embryo transferred.

Table V Multivariable Logistic Regression Model of the probability of a live birth after first cycle of IVF

	Per cycle	Per oocyte retrieval	Per embryo transfer
Intercept	-1.4426	-1.2229	-0.9500
Pregnancy rate (%) [a]	19.1	22.7	27.9
Smoking			
No	1	1	1
Yes	0.72 (0.61 – 0.84)	0.74 (0.63 – 0.87)	0.73 (0.62 – 0.86)
Age			
< 35 yrs	1	1	1
≥ 35 yrs	0.80 (0.67 – 0.96)	0.83 (0.69 – 1.00)	0.83 (0.69 – 1.00)
Body mass index (kg/m^2))			
20-27	1	1	1
< 20 kg/m^2	0.99 (0.82– 1.19)	0.97 (0.80– 1.17)	0.97 (0.80– 1.18)
≥ 27 kg/m^2	0.67 (0.48 – 0.94)	0.72 (0.51 – 1.02)	0.73 (0.52 – 1.03)
Unexplained subfertility	1	1	1
Tubal pathology	0.86 (0.70 – 1.01)	0.86 (0.71 – 1.05)	0.81 (0.66– 0.99)
Male subfertility	0.70 (0.57 – 0.86)	0.69 (0.56 – 0.85)	0.93 (0.75 – 1.16)
Other known factor	0.92 (0.68 - 1.23)	0.94 (0.70 – 1.27)	0.92 (0.68 – 1.25)
Secondary subfertility	1	1	1
Primary subfertility	0.96 (0.81 – 1.15)	0.96 (0.81 – 1.15)	0.99 (0.83– 1.16)
Period of IVF			
< 1990	1	1	1
≥ 1990	1.54 (1.18 – 2.02)	1.36 (1.03 – 1.79)	1.24 (0.4 – 1.5)
Duration of subfertility			
< 8 yrs	1	1	1
≥ 8 yrs	0.79 (0.62 – 1.00)	0.84 (0.66 – 1.08)	0.90 (0.70 – 1.16)

Values are odds ratios (95% confidence intervals) unless otherwise indicated.

[a] Calculated pregnancy rate.

The final model to calculate the pregnancy rate (PR) is shown below. All variables are indicators:
ln ((Pr / 1-Pr)) = -1.4426 – 0.3285 smoking – 0.2231 age ≥35 – 0.010 BMI <20 – 0.4005 BMI ≥27 – 0.1508 tubal pathology – 0.3567 male subfertility – 0.0834 other factor – 0.041 primary subfertility + 0.0432 treatment ≥ 1990 – 0.236 duration of subfertility ≥ 8 years.

Results

Population

The study population consisted of 8457 women who underwent their first cycle of IVF. The characteristics of the women are presented in Table I. Education was comparable to the Dutch population of women of childbearing age in the period studied and the different education levels were equally represented in all subfertility categories. There was no difference in duration of subfertility before the first treatment between the major subgroups we analysed. Of all women, 43% smoked during the first IVF attempt. Fifty-one percent of the women with tubal pathology smoked at the time of the first attempt, which was significantly more than in the other diagnostic groups. No significant differences in the distribution of extreme over- or underweight women between diagnostic categories were observed. Women with tubal pathology were significantly more secondary subfertile.

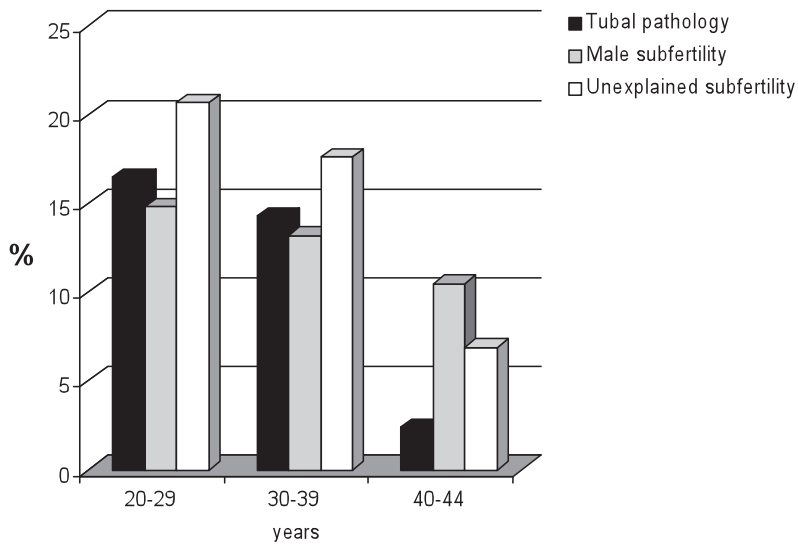
Cycles

The characteristics of the first IVF cycles of our population are described in Table II. The outcome of the first cycles in women with a main diagnosis of tubal pathology (3008 cycles), male subfertility (2179 cycles) and unexplained subfertility (1828 cycles) were analysed, using various outcome measures. Cycles with other known causes of subfertility (611), were also examined. The proportion of first cycles with TFF was 27.1% in the male subfertility group. This was significantly higher than for unexplained subfertility and tubal pathology, (10.6 and 7.3%, respectively). The abortion rate was significantly lower in the male subfertility group compared to both other indication categories. The overall proportion of first cycles with complications after IVF treatment (excluding TFF) was 4.9%. Ectopic pregnancies occurred significantly more often in the group with tubal pathology, compared to the other groups. The percentage of cycles with OHSS leading to hospitalization was significantly higher in the "other known" indication group (including PCOS) compared to the main indication categories.

The average number of embryos per transfer was 2.2 [0-7, median 2]. The overall live birth rate per cycle was 15.2%. The live birth rate per first cycle for the unexplained subfertile couples was higher (17.8%) in comparison with tubal pathology (14.6%) and male subfertility (13.6%). The live birth rates according to age and diagnostic categories are shown in Table III. For male subfertility there was no significant difference in the live birth rate per embryo transfer, in comparison with the unexplained subfertile couple (21.3% and 22.7%). Tubal pathology was associated with the lowest live birth rate per embryo transfer (18.4%). The overall implantation rate per cycle was 10.7%.

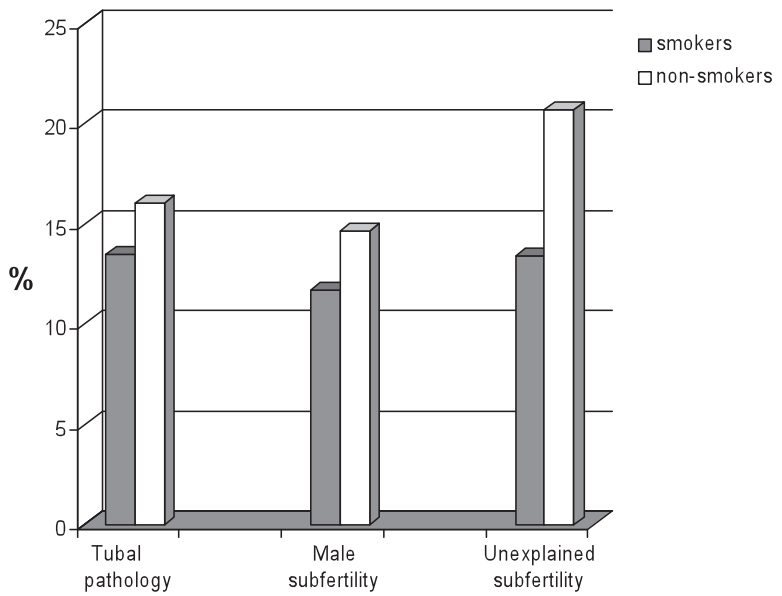
For the three major subfertility causes analysed, we found evidence of a clear and significant ($p < 0.001$) trend of declining live birth rates with increasing female age (Figure 2). The overall live birth rate per cycle decreased with 2% (p=0.03) for each additional year of the female age.

Figure 2 IVF live birth rate by cause of subfertility, for three age groups; % = proportion of first cycles resulting in a live birth. P-value for age effect p< 0.001



We compared the effects of smoking and BMI per diagnostic category in Table IV. In all subgroups according to subfertility diagnosis, the delivery rate for non-smoking women was significantly (p< 0.0001) higher than for smoking women (Figure 3). The effect of smoking was the largest for women with unexplained subfertility; smoking decreased the live birth rate with 7.3% compared with decreases of 3.0% and 2.5% for women with male subfertility and tubal pathology, respectively. Overall we found a non-significant difference between the mean number of oocytes for non-smokers (9.6 oocytes per cycle) compared to smoking women (9.0 oocytes per cycle) (95% CI: 0.35-1.0). Although the mean number of embryo's replaced for smoking women was higher (2.2 embryo's per transfer) compared to non-smoking women (2.14 embryo's per transfer), this led to lower pregnancy rates for smoking women. The abortion rate per pregnancy was significantly higher for smoking women compared to

Figure 3 IVF live birth rate for smoking and non-smoking women, by cause of subfertility; %= proportion of first cycles resulting in a live birth. P-value for smoking effect p< 0.001



non-smoking women respectively 21.4% and 16.4% (p=0.02). The ectopic pregnancy rate for both smoking as non-smoking women was not significantly different, respectively 3.8% and 2.9% per pregnancy (p=0.3).

There was a significantly higher live birth rate per cycle in women with normal weight (BMI ≥ 20 - 25 kg/m^2) and slight overweight (BMI 25 - 27 kg/m^2) compared with women with evident overweight with a BMI ≥ 27 kg/m^2. The unfavourable effect of overweight was largest for women with unexplained subfertility. Underweight women had similar live birth rates compared to women of normal weight.

Table V shows the results of multivariate analyses of predictors of the live birth rate as a result of the first IVF cycle, after successful ovum pick up and after embryo transfer. The first row gives the intercept, and the corresponding live birth rate for those with reference values for all variables. In the other rows, odds ratios are presented. These can be interpreted as follows: the live birth rate of smokers decreased with 28% compared with the live birth rate of

non-smokers, adjusted for the following confounders: age, BMI, indication for IVF, previous pregnancies, duration of subfertility and calendar period in which IVF took place. There was only a significantly lower live birth rate per treatment cycle by cause of subfertility for couples with male subfertility. We found that the adjusted effect of smoking on the live birth rate was even stronger than an increase in female age with > 10 years, from age 20 to 30 years, with an OR of 0.78 (95% CI 0.63-0.96). The strength of the association with smoking differed between the subfertility groups. As in in the univariate analyses smoking was most deleterious to the couples with unexplained subfertility, and least to those with tubal pathology (Table IV). Overweight women (BMI > 27 kg/m^2) had a 33% reduced chance of a live birth in their first IVF cycle. As for smoking, the association with overweight was strongest in women with unexplained subfertility. BMI and age were both also included as continuous variables. The effect estimates were similar for live birth rate per cycle, per ovum pick-up and per embryo transfer: BMI per unit OR = 0.98 (0.95-1.00) and age per year OR = 0.98 (0.96-1.00). Women with primary subfertility had the same live birth rate as women with secondary subfertility. The duration of subfertility did not influence the live birth rate for the three major subfertility categories, even after 8 years of subfertility no significant decrease in live birth rate could be detected.

Discussion

In this large nationwide dataset we found that the live birth rate for male subfertility was significantly lower compared to unexplained subfertility and tubal pathology. Advancing female age had an unfavourable effect on the success rate of IVF for all subfertility causes. Smoking and overweight during IVF treatment had deteriorating effects on the live birth rates. Women who smoked had a significantly higher abortion rate than non-smoking women. Furthermore the effect of smoking was comparable to an increase in female age with 10 years, from age 20 to 30 years.

When interpreting our results the strengths and limitations of our study must be considered. Advantages of our analyses include the large size of the study population and the availability of near complete information on details of IVF treatment from the medical records and outcome of all pregnancies from the women themselves. A limitation of our study is that the analyses had to be based on women who responded to the questionnaire (a 71% response rate). Women who had a live birth after IVF were possibly more likely to participate to the OMEGA project, than those who remained childless. From two participating hospitals, a non-responder analysis to the questionnaire was performed. Indeed, we observed a higher response rate among women who had a live birth after IVF, compared to women who did not

(response rates of 73% and 64%, respectively). This might have resulted in a slight over-estimation of live birth rates after IVF in Tables II-IV. However, assuming that non-response was not associated with life style factors, the estimate of the OR is unbiased. For 3227 IVF treated women who returned the questionnaire, data from the medical files could not yet be obtained. Since this was due to limited project funding resulting in a random sample of records not yet completed, it is highly unlikely that this has led to selection bias. Another restriction of our study is that we should take into account that the success rates in these older data might differ from the success rates today (Kremer *et al.*, 2002). Unique of our analyses is that we were able to study the separate and combined influences of smoking and BMI for a very large number of IVF treatments.

Most of our results correspond with the results of the study of Templeton *et al.* (1996). We found that only male subfertility was associated with a significantly lower delivery rate per cycle compared with tubal pathology and unexplained subfertility. If we considered the delivery rates per embryo transfer, i.e., after fertilization had occurred, we did not observe a difference between unexplained subfertility and male subfertility. The abortion rate was significantly lower in the male subfertile group. These results imply that the receptiveness of the women with unexplained subfertility and male subfertility was at least the same, and probably better in the male subfertile group. For tubal pathology the delivery rate was significantly lower given an embryo transfer, compared to unexplained subfertility and male subfertility. The explanation for this difference could be the negative effect of tubal pathology on the implantation processes and the embryotoxicity of hydrosalpinx fluid (Johnson *et al.*, 2002).

Individual studies comparing smoking and non-smoking women undergoing IVF treatment do not always indicate a decreased live birth rate with smoking. A meta-analysis (Augood *et al.*, 1998) showed that women who smoked had significantly lower pregnancy rates per IVF treatment compared to non-smokers. However, in none of these studies, a subdivision was made according to the indication for IVF and each of the studies reported different confounding factors and calculated odds ratios using different statistical methods. In a review (Zenzes, 2000) on the genetic damaging effects from smoking and its components on germinal cells, evidence was found that smoking affected the quantity and quality of oocytes and that it leads to an early age of menopause. Our results show a lower live birth rate and higher abortion rate for smoking women unless they had a higher mean number of embryos transferred. This might explain the lower quality of these embryos.
We studied the effects of both smoking and age on the live birth rate and found a trend of decreasing live birth rates with increasing age, which was consistently lower for smokers. Among women with tubal pathology, the diagnostic group with significantly more smokers than in the other subfertility causes, we found that the deteriorating effect of smoking on the

live birth rate per embryo transfer was not as strong as among women in the other diagnostic categories. The difference in influence of smoking on the outcome of pregnancy per indication category was not statistically significant (Breslow-Day test for homogeneity of odds ratios p=0.19).

There is a clear association of an increased BMI, risk of complications during pregnancy and a higher chance of abortion and subfertility (Norman and Clark 1998; Wang *et al.* 2000; Wang *et al.* 2002). After multivariable logistic regression modelling, we also found a significant effect of overweight (BMI ≥ 27 kg/m^2) on the live birth rate per cycle, with an OR of 0.67 (95% CI 0.48 – 0.94).

Besides dependency on calendar period, prognostic models for IVF depend on the success rate of the treating hospital (Haan *et al.*, 1991; Templeton *et al.*, 1996; Kremer *et al.*, 2002) patient characteristics and the number of previous IVF cycles (Tan *et al.*, 1996; Templeton *et al.*, 1996; de Mouzon *et al.*, 1998). Publications suggest constant success rates for each of the first three cycles (Haan *et al.*, 1991; de Vries *et al.*, 1999). Some attribute this to active censoring, which leads to withdrawal of couples with poor prognosis (Land *et al.*, 1997). In our study, continuation of IVF treatment depended on indication, due to the differences in fertilization rate. Twenty-five percent of the couples diagnosed with male subfertility did not complete three cycles and remained childless as compared with 13% of couples with unexplained subfertility and 5% of couples with tubal pathology. For reasons of comparability we therefore restricted our analyses in the present study to the first IVF treatment cycle only.

Our historical cohort study enables us to assess the differences in success rates of IVF between the various subfertility causes. However, to study the efficacy of IVF in various diagnostic categories, a long-term clinical trial will be the best option, comparing the pregnancy rates of IVF or ICSI treatments with no treatment. A second best option is the comparison of the spontaneous pregnancy rate in subfertile couples on the waiting list for IVF or ICSI, with the results of IVF or ICSI treated couples. We are expecting results from such a study in the Netherlands in the near future.

In conclusion, we observed differences in success rate between subfertility causes in favour of unexplained subfertility. Smoking had an unfavourable effect on the outcome of IVF and was comparable with an increase in female age of more than 10 years from age 20 to 30 years. Overweight had a strong harmful effect on the live birth rate after IVF. The effect of smoking and overweight was largest among women with unexplained subfertility. These results suggest that women, and in particular those with unexplained subfertility, may be able to improve the outcome of subfertility treatment by quitting smoking and losing weight.

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5

Chapter | 6

Spontaneous pregnancies after IVF: influence of patient characteristics and lifestyle

6

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Abstract

Background: To predict the chance of a spontaneous conception leading to a live birth after IVF, based on prior subfertility treatment and lifestyle factors.

Methods: Historical cohort study of 8669 women who received IVF treatment in one of the 12 IVF centres in the Netherlands between 1983 and 1995. The probability of a spontaneous conception leading to live birth within 12 months after an unsuccessful last IVF, or within 12 months after an IVF live birth.

Results: In total, 1065 women had at least one spontaneously conceived live birth after a median follow-up of 5 years. Within the first year after IVF treatment, or 12 months after an IVF pregnancy, or IVF live birth, 613 women had a spontaneous pregnancy leading to a live birth. For women with no pregnancy after last IVF treatment, the chances of a spontaneously conceived live birth decreased with older age (OR 0.94 per year, 95% CI 0.91 - 0.98), with a duration of subfertility ≥ 6 year (OR 0.80, 95% CI 0.61 – 1.1), and with the number of IVF attempts ≥ 4 (OR 0.71, 95% CI 0.49 – 1.1), but increased with male, unexplained, or other subfertility causes (OR 1.5, 95% CI 1.0 – 2.2), (OR 2.0 95% CI 1.3-3.2), and (OR 1.9, 95% CI 1.3 - 2.8), respectively, compared to tubal pathology. Several lifestyle factors unfavourably affected the chances of a spontaneously conceived live birth: BMI ≥ 27 kg/m^2 (OR 0.47, 95% CI 0.31 – 0.71), smoking (OR 0.72, 95% CI 0.54 - 0.94), ≥ 4 units of caffeine/day (OR 0.72, 95% CI 0.55 - 0.93), and ≥ 3 units of alcohol/week (OR 0.57, 95% CI 0.42 – 0.78).

Conclusions: Within one year after last IVF, or within one year after an IVF pregnancy or an IVF live birth, 7% of all women had a spontaneous conception leading to a live birth. The impact of subfertility-related factors and lifestyle on the chances of pregnancy before and during IVF, also applies to the chances of a spontaneous conception after IVF treatment.

Introduction

A spontaneous pregnancy is still possible after a long period of subfertility, even after unsuccessful IVF or ICSI. So far, studies on spontaneous pregnancies after IVF or ICSI treatment had small sample sizes. Most studies consisted of selective observations, because only couples with IVF resulting in a live birth were included (Hennelly *et al.*, 2000, Shimizu *et al.*, 1999). Other studies investigated only one cause of subfertility, such as severe male subfertility, after discontinuation of ICSI (Almagor *et al.,* 2001, Osmanagoaglu *et al.,* 2002, Ludwig *et al.,* 2008). To our knowledge, there is only one small (n= 116) study on the overall likelihood of spontaneous pregnancy after successful and unsuccessful IVF for all causes of subfertility (Cahill *et al.*, 2005). A spontaneous pregnancy rate of 18% up to 3 years after last treatment was reported. In none of these studies, however, lifestyle factors were considered, although these may influence pregnancy rates. A negative impact on the time to pregnancy for non-subfertile couples trying to conceive was found for smoking, caffeine use, and overweight of women, and for alcohol intake of men (Hassan and Killick 2004, Bolúmar *et al.*, 2000). These factors are likely equally important after IVF treatment.

The aim of this study was to predict the likelihood of a spontaneous conception leading to live birth, both after successful and unsuccessful IVF treatment, taking into account female age, pregnancy history, duration and cause of subfertility, the number and outcome of the preceding IVF treatments, Body Mass Index (BMI), smoking, and caffeine and alcohol use.

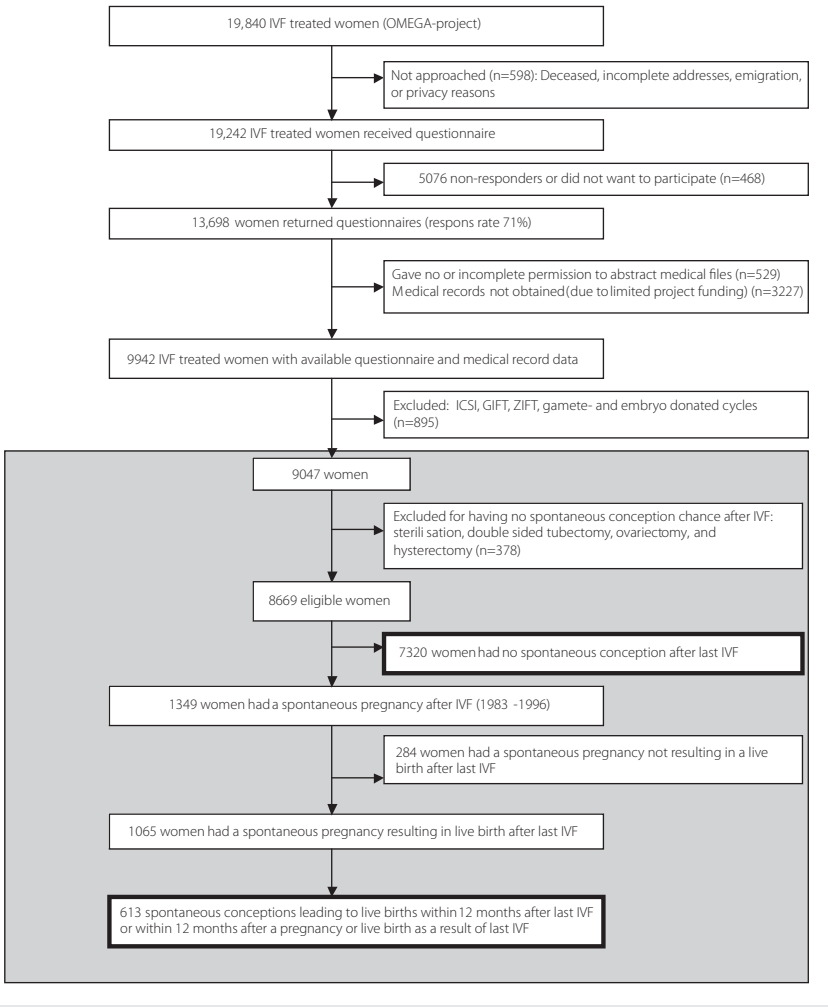
Methods

Design

Data were obtained from a large nationwide historical cohort study set up in 1996, including 19,840 subfertile women who had at least one IVF treatment in one of the 12 IVF centres in the Netherlands in the period 1983-1995 (The OMEGA–project, Klip *et al.*, 2001, Lintsen *et al.*, 2005), see Figure 1. From 1996-2000, 19,242 women were sent a 23-page questionnaire about their history of subfertility treatment, spontaneous conceptions, months of breastfeeding following each delivery, and lifestyle factors. The response rate to the questionnaire was 71%.

From 1996 to 1999, data were extracted from the medical records in the IVF centres. Due to limited funding, the records of 3227 women who had returned the questionnaire, could not be abstracted. Bias is unlikely, however, as there was no selection on the patient level. ICSI treatments carried out from 1992 and during the first years only in small numbers, were excluded from analyses. Also special IVF related treatments (GIFT, ZIFT), and cycles with gamete or embryo donation were excluded.

Figure 1 Flow chart of IVF patients in the OMEGA-study and of participants of the study on spontaneous pregnancies after IVF (grey area). Analyses were carried out with the data presented in the bold marked blocks



Participants

The IVF treatment data from the medical records were combined with information from the questionnaires for 9047 women, outlined in the grey area of Figure 1. Women with absolutely no chance of a spontaneous pregnancy were excluded: women with a history of sterilisation without refertilisation, double-sided tubectomy, bilateral ovariectomy, or hysterectomy after

IVF (n=378). Women were included in the analyses only once, meaning that only the first spontaneous pregnancy after IVF was studied.

Follow-up

The maximum follow-up duration from last IVF treatment until the questionnaire was 13 years, the median interval was 5 years and the interquartile range 3-6 years. With a long follow-up, the chance of an alteration in the fertility situation increases, e.g. through a divorce, remarriage, and conception with another partner. Therefore, we only included spontaneous pregnancies within an interval of 12 months after last IVF. In case the last IVF had resulted in a pregnancy and a live birth, the follow-up of 12 months started after delivery taking into account months of exclusive breast feeding. In case an IVF pregnancy ended in a miscarriage, the follow-up started 3 months after IVF, the average period of having a miscarriage followed by low fertility because of cycle recovery.

Prognostic factors

Prognostic factors were: the age of the patient at last IVF and was extracted from the medical files, the most important causes of subfertility of the couple (including tubal pathology, male related subfertility, unexplained subfertility, and other causes of subfertility, such as hormonal disturbances, cervical hostility, uterine pathology, and endometriosis), primary or secondary subfertility (primary: no pregnancy before the IVF referral), and duration of subfertility, defined as the time from child wish before the first contact with the general practitioner or gynaecologist until last IVF treatment (cut of point at 6 years). Height, weight, and lifestyle-related factors were extracted from the questionnaires. Based on the literature and the distribution of these variables in our data, caffeine and alcohol use were dichotomized with cutoff values of 4 or more units of coffee or tea per day and 3 or more units of alcohol per week. Women who smoked more than one cigarette per day for at least one year during the follow-up period were defined as smokers. Because the number of obese women was small (n=696, 8% of all eligible women), we did not classify the BMI according to the WHO criteria (< 25 normal weight, 25-30 overweight, and obese > 30 kg/m^2), but used the same classification as in a former paper (Lintsen *et al.*, 2005): underweight, BMI < 20 kg/m^2 normal weight, BMI 20-27 kg/m^2 and overweight, BMI ≥ 27 kg/m^2. Unknown variables were included as missings.

Statistical analyses

The statistical analyses were performed using the statistical package SPSS 17.0. The association between each prognostic factor and the chance of a spontaneously conceived live birth after IVF was studied by means of logistic regression analysis, resulting in crude odds ratios (ORs) with 95 percent confidence intervals (95% CIs). After univariable analyses, we performed a multivariable regression analysis. The impact on the outcome: spontaneous pregnancy

after IVF, was assessed considering multiple independent variables. Backward selection was used with a significance level of $p < 0.15$ for keeping a factor in the model. The results of the multivariable regression analysis were converted into a ready-to-use chart for clinicians, to calculate the chance of a spontaneously conceived live birth within 12 months after last IVF treatment for a certain couple. To provide the internal validity of the resulting prediction model the bootstrap method (taking samples with replacement from the original data mimicking the situation that the study had been repeated multiple times) was used with 100 replications. From this procedure, the amount of over-fitting of the model was assessed and a 'shrinkage' factor was derived; for optimal prediction in future patients, the odds ratios of the model should be adjusted with this shrinkage factor (van Houwelingen and Le Cessie, 1990). The discriminative ability of the model was assessed by the *c*-statistic, and a correction for optimism was applied. The c-statistic equivalent to the AUC (Area Under an Receiver Operating Characteristic Curve), measures how well the model would be able to make a distinction between couples who may have a spontaneously conceived live birth after IVF and couples who may not conceive spontaneously after IVF (Harrell *et al.,* 1996).

Results

Of the 8669 subfertile women who received one or more IVF treatments between 1983 and 1995, 1349 women, with a median follow-up period of 5 years, had at least one spontaneous pregnancy after last IVF. For 1065 women (79%), this spontaneous pregnancy resulted in a live birth of whom 613 women conceived spontaneously within 12 months after last IVF

Table I Characteristics of women in the OMEGA-cohort with no spontaneous pregnancy after IVF, compared to women who had a spontaneous conception leading to live birth within 12 months after last unsuccessful IVF or within 12 months after IVF pregnancy or delivery

	No spontaneous conception after IVF	Spontaneous conception resulting in live birth after IVF
No. of women	**7,320 (100%)**	**613 (100%)**
Age at last IVF (years), average (SD)	34.1 (4.0)	32.7 (3.7)
≤ 29	925 (12.6)	126 (20.6)
30-34	2,860 (39.1)	298 (48.5)
35-39	2,740 (37.4)	166 (27.1)
≥ 40	591 (8.1)	23 (3.8)
Missing	204 (2.8)	-

Subfertility history (%)		
Primary	3,997 (54.6)	384 (62.8)
Secondary	1,865 (25.5)	154 (25.1)
Unknown	1,458 (19.9)	75 (12.2)
Duration of subfertility (years), mean (SD)	6.6 (3.4)	5.5 (2.6)
< 6	3,070 (41.9)	321 (52.4)
≥ 6	2,148 (43.0)	198 (32.3)
Missing	1,102 (15.1)	94 (15.3)
Diagnostic category		
Tubal pathology	2,663 (36.4)	125 (20.4)
Male subfertility	2,008 (27.4)	189 (30.8)
Unexplained subfertility	1,803 (24.6)	208 (34.0)
Other known causes #	789 (10.8)	84 (13.7)
Unknown	57 (0.8)	7 (1.1)
Number of IVF attempts, mean (SD)	3.2 (2.2)	2.6 (1.7)
1	1,638 (22.4)	184 (30.0)
2-3	3,177 (43.4)	288 (47.0)
≥ 4	2,484 (33.9)	139 (22.7)
Missing	21 (0.3)	2 (0.3)
Pregnancy with last IVF		
No	4,759 (65.0)	386 (63.0)
Yes, miscarriage	217 (3.0)	18 (2.9)
Yes, live birth	2,150 (29.4)	209 (34.1)
Missing	194 (2.6)	-
BMI, mean (SD)	23.9 (4.0)	23.7 (3.6)
< 20	861 (11.8)	65 (10.6)
20-27	5,044 (68.9)	446 (72.8)
> 27	1,307 (17.9)	95 (15.5)
Missing	108 (1.5)	7 (1.1)
Smoking		
No	4,076 (55.7)	403 (65.8)
Yes	3,168 (43.3)	208 (33.9)
Unknown	76 (1.0)	2 (0.3)
Caffeine intake per day, mean (SD)	4.3 (1.6)	4.2 (1.5)
< 4	2,524 (34.5)	251 (40.9)
≥ 4	4,497 (61.4)	352 (57.5)
Missing	299 (4.1)	10 (1.6)
Alcohol intake per week, mean (SD)	0.5 (0.8)	0.4 (0.6)
< 3	4,443 (60.7)	437 (71.3)
≥ 3	2,210 (30.2)	154 (25.1)
Missing	667 (9.1)	22 (3.6)

Including: endometriosis and uterine, cervical, ovary and mixed reasons

treatment, or within 12 months after IVF pregnancy or delivery (see Figure 1). The overall probability of a spontaneously conceived live birth was 7% (613/8669), within 12 months after last IVF, or within 12 months after the IVF delivery.

After univariable analyses we found that on average, women with a spontaneous conception leading to live birth after IVF were younger, had a shorter mean duration of subfertility, less often had tubal pathology, had a lower number of IVF attempts, and more often had a live birth as a result of last IVF, compared to women with no spontaneous pregnancy after IVF. Furthermore, these women less often had a high BMI, were less often smokers, and drank less coffee or tea and fewer alcoholic drinks (Table I).

We developed two multivariable logistic regression models, one for women with no IVF pregnancy, and one for women who did conceive after last IVF using all relevant variables of the univariable analyses. Complete data were available for 4493 women. The impact of the prognostic factors on the probability of a spontaneously conceived live birth within 12 months after an unsuccessful last IVF, or 12 months after an IVF pregnancy, or IVF live birth are shown in Table II. The chance of a spontaneously conceived live birth for women with unsuccessful last IVF decreased with increasing maternal age (OR 0.94, 95% CI 0.91 to 0.98), Compared to tubal pathology, the chances of a spontaneously conceived live birth were increased for male-related subfertility, unexplained subfertility, and other known causes of subfertility (including endometriosis and cervical, uterine, and hormonal causes) with ORs of 1.48 (1.02 to 2.15), 2.00 (1.27 to 3.17), and 1.94 (1.34 to 2.80), respectively. Overweight (BMI ≥ 27 kg/m^2), smoking, drinking ≥ 4 cups of caffeine containing drinks daily, and drinking ≥ 3 units of alcohol per week reduced the chances of a spontaneously conceived live birth with ORs of 0.47 (0.31 to 0.71), 0.72 (0.54 to 0.94), 0.72 (0.55 to 0.93), 0.57 (0.42 to 0.78), respectively. For women with an IVF-live birth, lifestyle factors were no predictors in the multivariable analysis.

For the resulting prediction model, the c-statistic measuring the discriminative ability of the model was 0.68, and 0.66 when corrected for optimism. This indicates that the model would be able to separate women with a high chance of a spontaneous pregnancy from women with a low chance in 66% of the cases. The shrinkage factor determined by the internal validation procedure was 0.92, showing only slight overfitting. The reliability of the prediction of a spontaneous pregnancy leading to a live birth is evaluated by the calibration of the model, the degree to which the calculated probabilities agree with the observed spontaneous pregnancies (Coppus *et al.,* 2009). The calibration of the prediction model was added in Figure 2.

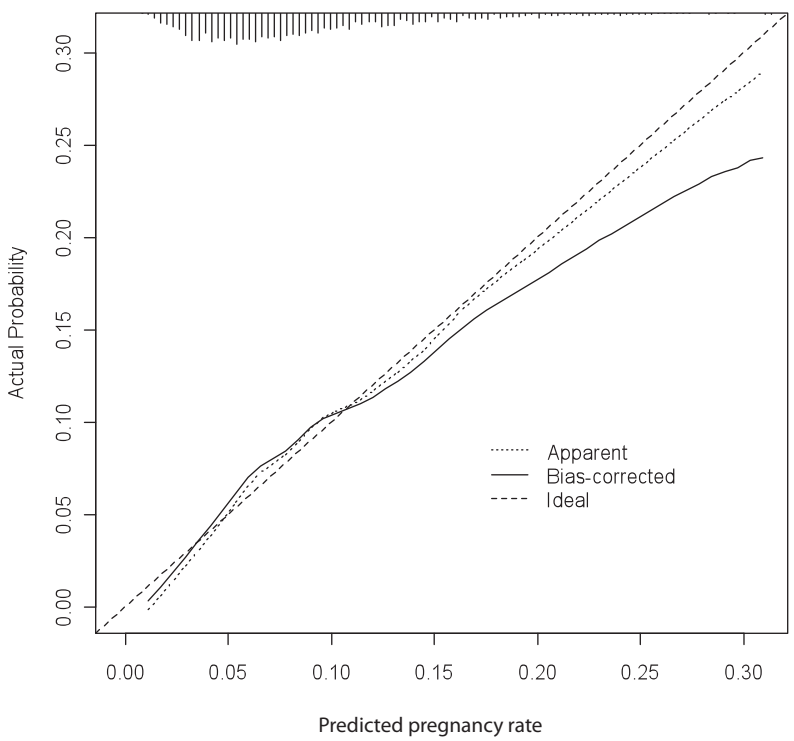
A score chart and a corresponding model is presented that can be used for an individual couple to calculate the chance of a spontaneous pregnancy resulting in a live birth within 12 months after last unsuccessful IVF (see Figure 3). The points given indicate the impact of the different factors. For example, a women of 37 years of age (-6 points), with more than 6 years

Table II Analyses of factors predicting a spontaneously conceived live birth after IVF within 12 months after unsuccessful IVF treatment or 12 months after IVF pregnancy or delivery

	Univariable	**Multivariable Adjusted No pregnancy with last IVF N=3,201**	**Multivariable Adjusted* Live birth with last IVF n=1,792**
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**
Age at last IVF (continuous)	0.92 (0.90-0.94)	0.94 (0.91-0.98)	0.94 (0.90-0.99)
Subfertility history (%)			
Primary	1.00 *(ref)*	1.00 *(ref)*	1.00 *(ref)*
Secondary	0.86 (0.71-1.04)	1.27 (0.95-1.70)	0.74 (0.50-1.08)
Duration of subfertility (years)			
< 6	1.00 *(ref)*	1.00 *(ref)*	-
≥ 6	0.60 (0.50-0.72)	0.80 (0.61-1.06)	
Cause of subfertility			
Tubal	1.00 *(ref)*	1.00 *(ref)*	1.00 *(ref)*
Male	2.01 (1.59-2.53)	1.48 (1.02-2.15)	1.68 (1.07-2.63)
Other	2.27 (1.70-3.02)	1.94 (1.34-2.80)	1.90 (1.23-2.93)
Unexplained	2.46 (1.95-3.09)	2.00 (1.27-3.17)	1.70 (1.00-2.92)
Number of IVF attempts			
1	1.00 *(ref)*	1.00 *(ref)*	1.00 *(ref)*
2-3	0.81 (0.66-0.98)	0.96 (0.69-1.33)	0.75 (0.52-1.07)
≥ 4	0.50 (0.40-0.63)	0.71 (0.49-1.05)	0.60 (0.38-0.94)
BMI (kg/m^2)			
20-27	1.00 *(ref)*	1.00 *(ref)*	
< 20	0.85 (0.65-1.12)	0.92 (0.62-1.36)	-
≥ 27	0.82 (0.65-1.03)	0.47 (0.31-0.71)	
Smoking			
No	1.00 *(ref)*	1.00 *(ref)*	-
Yes	0.66 (0.56-0.79)	0.72 (0.54-0.94)	
Caffeine (cups per day)			
< 4	1.00 *(ref)*	1.00 *(ref)*	-
≥ 4	0.79 (0.67-0.93)	0.72 (0.55-0.93)	
Alcohol (units per week)			
< 3	1.00 *(ref)*	1.00 *(ref)*	-
≥ 3	0.71 (0.59-0.86)	0.57 (0.42-0.78)	

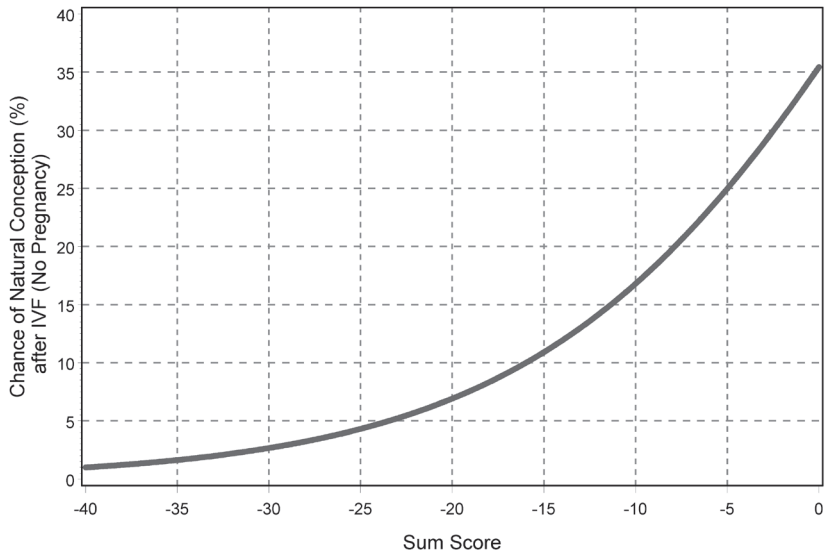
*The probability for keeping variables in the model was $p < 0.15$.
For women with a live birth with IVF, duration of subfertility, BMI, smoking, caffeine and alcohol use are no predictors in the multivariable data analyses. The lifestyle variables, BMI, smoking, caffeine and alcohol use entered in the analysis are the values recorded after a the whole interval of follow-up (median 5 years).

Figure 2 Calibration plot with calculated probability and observed (actual) probability of a sponaneous conception leading to a live birth after discontinuation of IVF treatment. The plot shows that the model tends to overstimate the probablilities



(-2 points) of unexplained subfertility (0 points), after 3 IVF attempts (0 points), with overweight (-6 points), smoking (-3 points), drinking more than 4 cups of caffeine holding units (-3 points) and more than 3 glasses of alcohol per week (-5 points), has a sum score of -25 points and thus around 5% chance of a spontaneously conceived live birth. A women with the same age, cause, pregnancy history, and duration of subfertility, but with normal weight, non-smoking and drinking less than 4 cups of coffee or tea a day, and less than 3 units of alcohol per week has a sum score of -8 points and a 18% chance of conceiving spontaneously within a year after last IVF.

Figure 3 score chart with corresponding curve toe calculate the chance of a spontaneous conception leading to a live birth within 12 months after a unsuccessful IVF



Biological factors

Age (year)	Points	Duration Subfertility (year)	Points	Cause of subfertility	Points	Number IVF attempts	Points
≤25	0	< 6	0	Tubal pathology	-6	1	0
26	0	≥ 6	-2	Male subfertility	-3	2-3	0
27	-1			Unexplained	0	≥ 4	-3
28	-1			Other known causes	0		
29	-2						
30	-2						
31	-3						
32	-3						
33	-4						
34	-4						
35	-5						
36	-5						
37	-6						
38	-6						
39	-7						
40	-7						
41	-8						
42	-8						
43	-9						
44	-10						
≥45	-10						

Life -style factors

BMI	Points	Smoking	Points	Caffeine intake (cups a day)	Points	Alcohol intake (glasses a week)	Points
< 20	-1	No	0	< 4	0	< 3	0
20-27	0	yes	-3	≥ 4	-3	≥ 3	-5
≥27	-6						

Discussion

We conducted a study on subfertility related factors and the chances of a spontaneous pregnancy after IVF on a large data base. We also studied the impact of lifestyle factors on the spontaneous pregnancy chance after termination of IVF.

After IVF, within a year of last treatment, or within a year after an IVF pregnancy, or IVF delivery, 7% of all women had a spontaneous pregnancy leading to a live birth, taking into account extra time for a miscarriage, delivery, and breastfeeding. We built a model to predict an individual couple's chance of a spontaneous conception leading to live birth after unsuccessful IVF. The probability of a spontaneously conceived live birth after IVF decreased with increasing female age, with a long duration of subfertility, after multiple IVF attempts, with overweight, smoking, and high caffeine and alcohol intake. The cause of subfertility also influences the chance of conceiving spontaneously after IVF, with negative effects of tubal pathology.

Comparable to a previous report (Cahill *et al.,* 2005), we observed a 16% chance of a spontaneous pregnancy after a long follow-up interval (1349/8669). We also confirmed that the highest chance of a spontaneous pregnancy occurs within the first year after last IVF (Cahill *et al.,* 2005, Roh *et al*., 1987). In a study among fertile couples trying to conceive without fertility treatment, adverse effects on the interval leading to pregnancy were observed for heavy smoking of both women and men, caffeine use and overweight of women, and heavy alcohol intake of men (Hassan and Killick, 2004). We found comparable unfavorable effects on the chances of a spontaneous pregnancy after unsuccessful IVF, but already at lower cutoff values for these variables. Conceivably, the detrimental impact of unhealthy lifestyle habits is stronger for subfertile couples. On the other hand, a pregnancy with IVF treatment, overruled the variables for lifestyle in the model.

The chance of a spontaneous pregnancy resulting in a live birth within the first year *after* IVF was 7%. In a previous study, we found a one year cumulative chance of 9% for an ongoing spontaneous pregnancy *before* IVF or ICSI treatment whilst on the waiting list (Eijkemans *et al.,* 2008). These spontaneous pregnancy chances before and after IVF seem comparable, although the difference between the populations included in both studies has to be mentioned. In this study of spontaneous pregnancies after IVF, we excluded women who had definitely no chance of a spontaneous pregnancy (e.g. double sided tubectomy) and ICSI treatments. In the study of spontaneous pregnancies before IVF/ICSI, on the other hand, all forms of tubal pathology were included and the male subfertile group included both mild (IVF) and severe (ICSI) semen pathology.

The results of our analyses are based on data from IVF treatments between 1983-1995, this may affect the extrapolation to current practice. E.g. IVF treatment results have increased since, which might lead to lower chances of spontaneous pregnancy. Although, we could not confirm this hypothesis with the following analysis: the pregnancy rates before and after

1990, the start of standard use of LHRH analogues, did lead to overall higher IVF pregnancy rates, but the spontaneous pregnancy rate before and after 1990 did not change.

The data on lifestyle factors used in the analyses are those reported in the self-administered questionnaires. For instance, the body weight reported at the moment the questionnaire was filled out, was used in the analyses. We acknowledge that this could have been different at the time the spontaneous pregnancy occurred, and also recall bias could have influenced the results. Further, for the classification of BMI we did not use the WHO classification. The number of women with high BMI were too low, but even at the lower cutoff level that we used, the effect of overweight on the chance of a spontaneous pregnancy was found.
In general, the use of unfavorable lifestyle factors may be underreported. As a result, the associations that we observed with spontaneous pregnancy chances may in fact reflect higher average levels of use.
For important life events, such as pregnancies, however, it is highly likely that the data on the questionnaires are reliably recorded. Furthermore, couples treated for fertility problems are known to be a well-motivated population and they appear to have a high sensitivity and specificity for self-report as well (Olsen *et al.*,1997, de Boer *et al.*, 2005).

In 2006, preparatory for the study on spontaneous pregnancy chances after IVF, we carried out an additional pilot study among almost 500 women from this OMEGA dataset, who had at least one spontaneously conceived live birth after IVF. These women were sent a questionnaire on lifestyle, use of contraceptives, change of partner and child wish after IVF treatment. Strikingly, the use of caffeine and alcohol did hardly change over the years (comparing the answers on use of caffeine and alcohol in the OMEGA-data and the pilot). These lifestyle factors can be rightly named habits and did not change much over a longer time period. Furthermore, only 5% of the couples used contraceptives after IVF treatment, including the couples that did not have a child wish anymore. This illustrates the disbelief couples experience when a spontaneous pregnancy occurs after a long period of infertility and going through intensive fertility treatment.
Unfortunately, in the current dataset we were not informed about relationships that ended after IVF. Therefore, we decided to report on the spontaneous pregnancies after IVF within 12 months after treatment or 12 months after an IVF pregnancy, or IVF delivery, to reduce the chance of an alteration in fecundity, by change of partner, or not having a partner at all. Of course, even within 12 months after IVF, the ending of a relationships is possible, in particular after treatment failure. This could have biased our results in particular for those women without an IVF pregnancy. However, a comparison of the spontaneous pregnancy chance within 12 months after last IVF to the spontaneous pregnancy chance after complete follow-up for women with a male related cause of subfertility, a subgroup with the highest

chance of fecundity change, did not show a statistically significant difference (data not shown).

We may have underestimated the chance of a spontaneous pregnancy after IVF because only the first spontaneous pregnancy after IVF was included in the analyses. Furthermore, even without exclusive breastfeeding, fertility may not have returned in the first few months after delivery or women may not have resumed intercourse right away, leading to a shorter follow-up interval. Similar arguments may apply to women having had a miscarriage from an IVF pregnancy. In addition, some women may have started using contraceptives during follow-up.

The strengths of this study include the large cohort of women after successful and unsuccessful IVF treatment; the availability of near complete lifestyle data; and the reduction of the impact of male partner change by restriction of the analyses to a limited period after IVF. We feel that our results about spontaneous pregnancy chances after IVF are relevant for general practitioners and gynaecologists. However, validation of the model with new data is of course still necessary.

In conclusion, within 12 months after last IVF, or 12 months after an IVF pregnancy, or IVF-live birth, the chance of a spontaneous conception leading to a live birth was 7%. The impact of subfertility-related factors, such as the woman's age, the duration of subfertility, and the number of IVF attempts, on the pregnancy chances with IVF treatment (Templeton *et al.,* 1996, Lintsen *et al.,* 2007) also applied to the spontaneous pregnancy chance *after* IVF. The detrimental effects of overweight, smoking, and caffeine and alcohol use on the spontaneous pregnancy chance are demonstrated in subfertile couples after termination of IVF. With a prediction model including both lifestyle and reproductive factors, the chance to conceive spontaneously after IVF can be quantified.
Even after termination of an unsuccessful IVF treatment, couples should be aware that there is still a chance of a spontaneous pregnancy, and contraceptive use should be advised when a pregnancy is not wished for anymore. On the other hand, women should also be counseled about the possible effect of lifestyle changes that can influence their fecundity even after discontinuation of fertility treatment.

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Chapter | 7

Anxiety and depression have no influence on the cancellation and pregnancy rates of a first IVF or ICSI treatment

7

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Abstract

Background: After many years of research, the impact of psychological distress on the IVF treatment outcome is still unclear. This study aimed to determine the influences of anxiety and depression before and during IVF or ICSI treatment on the cancellation and pregnancy rates of inductees.

Methods: In a multicentre prospective cohort study, we assessed anxiety and depression at baseline and the procedural anxiety level one day before oocyte retrieval, with the short versions of the State Anxiety Inventory (STAI) and the Beck Depression Inventory-Primary Care (BDI-PC). The effect of baseline anxiety and depression on the cancellation and pregnancy rates of 783 women in their first IVF or ICSI treatment was evaluated. We also determined if a change in anxiety from the start of treatment until just before oocyte retrieval affects the pregnancy rate. The predictive value of distress was assessed while controlling for several factors in subfertility treatment.

Results: Neither baseline nor procedural anxiety, nor depression affected the ongoing pregnancy rates, with odds ratio's (ORs) of 1.04 (95% CI: 0.82-1.33), 0.96 (95% CI: 0.77-1.20), and 0.85 (95% CI: 0.65-1.10), respectively. Neither did the anxiety gain score affect the pregnancy rate, OR 1.08 (95% CI: 0.83-1.41). A cancellation of treatment could not be predicted by anxiety or depression, OR 1.16 (95% CI: 0.83-1.63) and 0.85 (95% CI: 0.59-1.22), respectively.

Conclusions: Inductees in IVF treatment can be reassured that anxiety and depression levels before and during treatment have no influence on the cancellation and pregnancy rates.

Introduction

Subfertility and stress are inextricably linked together. Women experience the period of long unfulfilled child wish, and the treatments that may arise from this need, as very stressful. The perception that stress has an adverse effect on the pregnancy chance has become widely accepted, but in spite of many years of research on psychological factors and IVF outcome, the results are still contradictory. Reviews have suggested a negative correlation between distress and IVF outcome (Eugster and Vingerhoets, 1999; Klonoff-Cohen, 2005; Campagne, 2006). However, most studies have shown methodological shortcomings, i.e. small samples, non-standardized psychological tests, different stages of sampling, and/or no discrimination between inductees and veterans. Additionally, except for women's age, other known confounding factors such as duration and cause of subfertility and pregnancy history were often not controlled for.

Stress before and during the IVF treatment is multidimensional. There is the chronic source of stress caused by the threat of the permanency of the infertility and loss of hope. Another source of stress is the prospect of the treatment itself. These sources of distress can be measured before treatment, by baseline anxiety and depression. In addition, the third source of stress is the actual participation in the treatment, which can be measured by the level of anxiety as a result of the threat of the treatment itself, the so-called procedural or situational distress at a certain point in time. It can be the fear for the daily hormone injections or a painfully oocyte retrieval, or the strain of the emotional moment at the embryo transfer.

Several prospective studies (with a range of women studied: between 40 and 291 inductees), have differentiated with standardized psychological tests, the influence of baseline anxiety or depression and/or procedural distress on IVF pregnancy chance: a high baseline distress level has negatively influenced the pregnancy rate in the study of Demyttenaere *et al.* (1992), Thiering *et al.* (1993), Klonoff-Cohen *et al.* (2001), Smeenk *et al.* (2001), Verhaak *et al.* (2001), Eugster *et al.* (2004) and in a large study of Boivin and Schmidt (2005) (818 couples, 75% were inductees). Conversely, baseline distress did not affect the pregnancy chance in the study of Merari *et al.* (1992), Boivin and Takefman (1995), Emery *et al.* (2003), Anderheim *et al.* (2005), and de Klerk *et al.* (2008). Indications of adverse effects of procedural stress, as measured by psychological or biological tests (e.g. hormone level), on the chance of IVF pregnancy were established by Boivin and Takefman (1995), Facchinetti *et al.* (1997), Gallinelli *et al.* (2001) and Smeenk *et al.* (2005). On the other hand, this influence was not found by Klonoff-Cohen *et al.* (2001), Lovely *et al.* (2003 and de Klerk *et al.* (2008). Contrary to all expectations, Merari *et al.* (1992) observed a significant higher state of anxiety level before oocyte retrieval for women who became pregnant. According to the study of Boivin and Takefman (1995), the period of

the highest stress level during an IVF treatment is measured between hCG administration and oocyte retrieval. Also the association of a lower adrenaline level at oocyte retrieval with an increased pregnancy chance observed by Smeenk *et al.* (2005) implicates that high anxiety levels shortly before oocyte retrieval might influence the implantation phase. To gain more insight into the interaction of stress and IVF treatment, we also studied if a change in anxiety, measured before treatment and just before oocyte retrieval, has a independent effect on the pregnancy rate. Furthermore, pre-treatment depression and anxiety scores have been related to the passive drop-out rate, concerning patients who voluntarily discontinue after first or subsequent treatment (Smeenk *et al.,* 2004). In this study, we assessed if basal psychological distress also has an association with unfinished, so-called cancelled treatments. By discriminating the influence of distress on the cancelled versus the non-cancelled cycles, we tried to distinguished the influence of distress on the stimulation phase versus the implantation phase.

In summary, so far studies on distress and IVF pregnancy are still inconclusive. The objective of this large prospective multicentre study with women having their first IVF or ICSI treatment is to determine the influence of distress at different points during treatment and with different end-points, while controlling for potential confounding factors in fertility treatment.

Materials and Methods

Design and subjects

We performed a prospective study in seven IVF clinics in the Netherlands: one university hospital and two general hospitals with licensed IVF laboratories, one satellite and three transport IVF-clinics. In the latter two types of clinics, the stimulation phase is started and the patients are referred to the licensed IVF centre for oocyte retrieval and/or embryo transfer. All new couples with an indication for IVF or ICSI treatment according to the IVF guideline formulated by the Dutch Society for Obstetrics and Gynaecology (NVOG, IVF guideline no 9, 1998, www.nvog.nl), could be asked by nurses and doctors involved in the research team if they wished to participate. In order to examine the influence of distress on the spontaneous pregnancy chance on the waiting list for treatment (a subject that goes beyond this paper), women were asked to participate in the study by completing three questionnaires on three different occasions. The first one was directly after IVF reference, when joining the waiting list before treatment (T0); the second questionnaire was one or two months before treatment, after pre-treatment information and instruction on self injection of the medication (T1), and the third questionnaire was one day before oocyte retrieval (T2). The time women had to wait on the waiting list differed between the clinics from 1 to 9 months. If there was no

waiting period, women skipped the questionnaire on T1, and the questionnaire on T0 was used. For the aim of this study, correlating psychological factors and the IVF cancellation and pregnancy rate, we used the second (time point T1 in IVF treatment) and the third (T2) questionnaires. Exclusion criteria were inadequate apprehension of the Dutch language and use of donor gametes.

This study was part of the national cohort study, on prediction of pregnancy chances with IVF and ICSI treatment, that was performed between 2002 and 2004 and published recently (IVF dataset: Lintsen *et al.,* 2007). The IVF outcome data and the fertility specific background variables such as pregnancy history, duration and cause of subfertility of all inductees participating to this study, as well as all other inductees, were registered in the national cohort study. The psychological dataset was matched with the IVF dataset of the seven participating hospitals.
The ethical committees of the participating clinics gave approval for the study.

IVF treatment

The treatment protocols were hospital specific, but all women were treated with conventional ovarian stimulation with gonadotrophins combined with a preceding pituitary down-regulation through a GnRH-agonist co-treatment. The oocyte retrieval was timed 34-36 h after administration of 5000 or 10 000 I U hCG. Fertilization was performed by standard IVF or ICSI technique. A maximum of two embryos were transferred. Luteal support was given by progesterone vaginally. Additional good quality embryos were cryopreserved and transferred in a later cycle if the treatment had been unsuccessful.

Distress measures

The baseline emotional status was defined in terms of state anxiety and depression. Anxiety was measured by means of the abridged Dutch version of the State Anxiety Inventory (STAI: Dutch translation: Spielberger, 1983; van der Ploeg *et al.,* 2000), by 10 items, out of 20, each ranging in score from 1 to 4. Each item has a four-point evaluation with a maximum sum score of 40, which indicates highest anxiety. Depression was measured using the short Dutch version of the Beck Depression Index for primary care (BDI-PC) (Beck *et al.,* 1997). The BDI-PC consists of 7, out of a total of 21 items ranging from 0 to 3, to indicate the severity of the symptoms. The maximum score could be 21. The questionnaires used have shown reliability and validity (Huiskes *et al.*, 1990a, b; Verhaak *et al.,* 2001, 2005, 2006). The questionnaire on T1, one or two months before the start of treatment, measured the baseline anxiety and depression status by asking how the participant has felt "the last week". The questionnaire on T2, one day before oocyte retrieval, measured the procedural state anxiety by means of the same abridged Dutch version of the STAI. The stress response to treatment was assessed by

comparing baseline anxiety at T1 with procedural anxiety at T2 and calculating the residual gain score indicating a change in anxiety by controlling for baseline anxiety. The different scales showed excellent reliability: anxiety alpha = 0.88; depression alpha = 0.82.

Definitions

Primary subfertility indicates that the woman had no pregnancy before referral to IVF. Duration of subfertility is defined as the time between the date of active child wish, or the date of last miscarriage, and the date of first IVF. The cause of subfertility contributing to the primary indication for IVF was divided into tubal, hormonal, unexplained, endometriosis, mild male-related subfertility, treated with IVF, and severe male subfertility, treated with ICSI. The first outcome measure was ongoing pregnancy after first IVF or ICSI treatment, confirmed by ultrasound of at least one fetus with positive heartbeat at 8 weeks gestation. A second outcome measure was cancellation of treatment, defined as having started stimulation without reaching oocyte retrieval.

Data analyses

Univariate frequencies and means of biological patient characteristics were calculated and compared between participants versus non-participants. Univariate frequencies of psychological scores at baseline were calculated for women with a cancelled cycle versus women who completed the first cycle, and psychological scores were compared between pregnant versus non-pregnant women. Multivariate logistic regression analyses were used to estimate the predictive effect of psychological scores on the probability of cancellation and of an ongoing pregnancy in non-cancelled cycles. The psychological scores were the baseline state anxiety and depression level at T1, the procedural state anxiety level at T2 and the residual gain score from T1 to T2. We adjusted for the following established variables: women's age, pregnancy history, cause and duration of subfertility (Stolwijk *et al.,* 1996; Templeton *et al.,* 1996; Lintsen *et al.,* 2007). All analyses were performed using SPSS 14.0. Statistical testing on all outcome measures was done at a 0.05 two-sided level of significance.

Results

Of 1124 eligible women 783 women filled in the first questionnaire before the treatment start (70% participation). Figure 1 provides a flowchart of the inclusion. For 78 women the treatment was cancelled before oocyte retrieval. 284 women did not complete, or forgot to bring along, the second questionnaire that had to be filled in one day before oocyte retrieval. We had complete follow-up of the first IVF or ICSI treatment for 421 women who filled in a questionnaire at T1 and at T2.

Figure 1 Flow chart of women starting their first IVF or ICSI treatment in one of seven IVF clinics between 2002-2003. The numbers in the shaded areas are used in the analyses

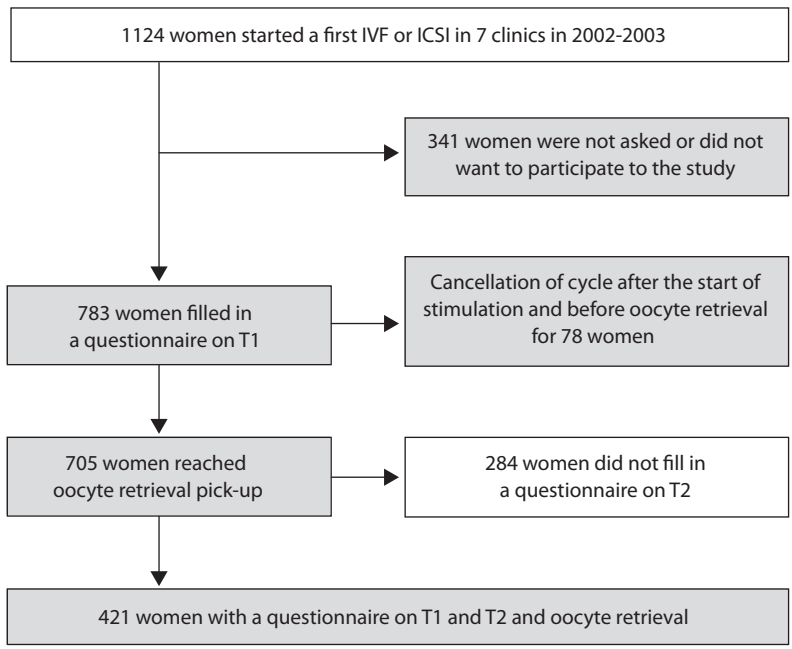

Table I presents baseline characteristics and main treatment outcomes of women at T1, of women who also contributed at T2, and of all other inductees in the period of study treated in one of the hospitals involved (non-participants to this study). Frequencies and means are equivalent for the three groups. The mean duration of subfertility was longer in the non-participating group.

Table II shows that there were no differences in the mean anxiety and depression levels at baseline and no differences in frequencies and means for biological variables for women who completed a first cycle and for women who did not reach the oocyte retrieval because of cancellation. Women with a cancelled cycle did have a longer mean duration of subfertility compared to women who completed the first cycle (3.9 years versus 3.3 years, p=0.02).

In Table III, the levels for anxiety and depression before and during IVF treatment and the anxiety gain score from pre-treatment to oocyte retrieval are shown to be not different for

Table I Characteristics of all women starting a first cycle of IVF or ICSI in 7 IVF clinics from 2002-2003

	Study participants with questionnaire on T1 (n= 783)	Study participants with questionnaire on T1 and T2 (n= 421)	Non-participants (n= 341)
Mean age (years) (SD) (range)	33.2 (3.7) (20.1-43.4)	33.2 (3.5) (23.5-42.4)	33.0 (4.3) (21.4-40.8)
Mean duration of subfertility (years) (SD) (range)	3.4 (1.9) (0.2-16.5)	3.3 (1.7) (0.2-13.7)	3.7 (2.3) *(0.3-18.7)
Pregnancy history (primary), % (n) [a]	69.7 (538)	72.0 (303)	65.0 (208)
Cause of subfertility, %(n) [a]			
Tubal pathology	15.2 (112)	12.7 (51)	15.5 (48)
Endometriosis	5.4 (40)	5.7 (23)	4.2 (13)
Hormonal	5.6 (41)	6.0 (24)	8.7 (27)
Male mild (IVF)	16.9 (124)	16.7 (67)	14.6 (45)
Male severe (ICSI)	37.1 (273)	40.8 (164)	42.4 (131)
Unexplained	17.0 (125)	15.9 (64)	10.0 (34)
IVF outcome, % (n) [a]			
Cancellation rate	10.0 (78)		9.7 (33)
Pregnancy rate	32.4 (252)	36.8 (154)*	31.9 (108)
Ongoing pregnancy rate	25.7 (197)	29.7 (122)*	26.7 (90)

[a] Percentages do not correspond to the numbers divided by the totals due to missing values.*$p < 0.05$. Only cycles with oocyte retrieval are included in the T1 and T2 group. For women on T1 (first column) and for the non-participants (third column), cancelled cycles are left in the analyses.

Table II Univariate analyses of psychological and biological factors predicting cycle cancellation at T1

		Not cancelled (n=705)	Cancelled (n=78)	P-value
T1	Basal State anxiety	17.7 (SD=4.9)	18.0 (SD=5.1)	0.68
T1	Depression	1.4 (SD=2.2)	1.3 (SD=2.0)	0.76
	Age (mean)	33.2 (SD = 3.6)	33.0 (SD = 4.5)	0.70
	Duration (mean)	3.3 (SD = 1.9)	3.9 (SD = 2.5)	0.02
	Primary, % (n) [a]	69.3 (483)	73.3 (55)	0.47
	Cause of subfertility [a]			1.00
	Tubal, % (n)	15.2 (101)	15.9 (11)	
	Endometrioses, % (n)	5.4 (36)	5.8 (4)	
	Hormonal, % (n)	5.6 (37)	5.8 (4)	
	Mild male (IVF), % (n)	17.0 (113)	15.9 (11)	
	Severe male (ICSI), % (n)	37.2 (248)	36.2 (25)	
	Unexplained, % (n)	17.0 (113)	17.4 (12)	

[a] Percentages do not correspond to the numbers divided by the totals due to missing values.

Table III Univariate analyses of psychological and biological factors predicting the IVF and ICSI ongoing pregnancy rate in patients having an oocyte retrieval

		Pregnant, Mean (SD)	Non-pregnant, Mean (SD)	P-value
T1	Basal State Anxiety [a]	17.6 (4.7) (n=196)	17.7 (5.0) (n=494)	0.74
T1	Depression	1.2 (1.8)	1.4 (2.4)	0.17
T2	Procedural State Anxiety [b]	18.4 (5.8) (n=122)	18.5 (5.8) (n=291)	0.82
T1 → T2	Anxiety gain score	0.9 (3.9)	0.8 (4.1)	0.73
	Age (mean)	32.9 (3.1)	33.4 (3.8)	0.09
	Duration (mean)	3.3 (1.7)	3.4 (1.9)	0.56
	Primary subfertility,% (n) [c]	71.0 (137)	69.0 (338)	0.61
	Cause of subfertility [c]			0.66
	Tubal, % (n)	15.6 (29)	14.6 (68)	
	Endometrioses, % (n)	3.2 (6)	6.2 (29)	
	Hormonal, % (n)	6.5 (12)	5.4 (25)	
	Mild male (IVF), % (n)	19.4 (36)	16.1 (75)	
	Severe male (ICSI), % (n)	36.6 (68)	37.6 (175)	
	Unexplained, % (n)	15.1 (28)	17.8 (83)	

[a]On T1 for 690 women data on IVF and psychological outcomes were complete. There were 15 missings in ongoing pregnancy; [b]On T2 for 413 women data were complete, there were 8 missings on ongoing pregnancy; [c]Percentages do not correspond to the numbers divided by the totals due to missing values.

Table IV Multivariate analyses for cancellation and ongoing pregnancy rate after oocyte retrieval for IVF or ICSI at T1

		Cancellation rate OR 95% CI (n=723)		P-value	Ongoing pregnancy rate OR 95% CI (n=644)		P-value
T1	Basal State anxiety [a]	1.16	0.83-1.63	0.38	1.04	0.82-1.33	0.74
T1	Depression [a]	0.85	0.59-1.22	0.39	0.85	0.65-1.10	0.21
	Age (per year)	0.96	0.89-1.04	0.30	0.95	0.90-1.00	0.07
	Duration (per year)	1.14	1.01-1.27	0.03	0.99	0.90-1.09	0.84
	Primary subfertility	1.24	0.68-2.26	0.49	1.10	0.74-1.65	0.63
	Cause of subfertility						
	Tubal (reference category)	1			1		
	Endometriosis	1.05	0.30-3.62		0.41	0.14-1.18	
	Hormonal	0.99	0.29-3.41	1.00	1.20	0.52-2.75	0.58
	Mild male (IVF)	0.87	0.35-2.17		1.15	0.63-2.10	
	Severe male (ICSI)	0.87	0.39-1.92		0.89	0.52-1.53	
	Unexplained	0.93	0.38–2.28		0.84	0.45-1.58	

[a]The odds ratio (OR) for the psychological variables corresponds to the relative change in odds on outcome when the variable is increased by 1SD.

pregnant compared to non-pregnant women. Pregnant women were younger than non-pregnant women, but the level did not reach significance.
We constructed a multivariate logistic regression model for the prediction of cancellation and the ongoing pregnancy rate with the basal anxiety and depression scores at T1 (Table IV). We also build a model for the prediction of the ongoing pregnancy chance with procedural anxiety at T2 and with the anxiety gain score from T1 to T2 (the latter two models not shown). In all models we adjusted for potential biological confounders: female age, pregnancy history, duration and cause of subfertility. Overall, as could be expected from the univariate results, neither baseline anxiety, nor depression showed influence on the cancellation rate, with ORs 1.16 (95% CI: 0.83-1.63), and 0.85 (95% CI: 0.59-1.22), respectively. The chance of cancellation could be predicted by a longer duration of subfertility, OR 1.14 (95% CI: 1.01-1.27). There was no influence of baseline, or procedural anxiety, nor of the anxiety gain score on the ongoing pregnancy rate, ORs 1.04 (95% CI: 0.82-1.33), 0.96 (95% CI: 0.77-1.20), 1.08 (95% CI: 0.83-1.41), respectively. Depression could not predict the pregnancy rate either, OR 0.85 (95% CI: 0.65-1.10). Pregnancy history, duration and cause of subfertility also had no influence on the pregnancy rate. With higher female age there was a trend towards a decreased chance of pregnancy, OR 0.95 (95% CI: 0.90-1.00), (p=0.07). The results didn't change if we used the composite score for anxiety and depression.

Discussion

In this large prospective multicenter study we examined the relation of anxiety and depression on the rates of cancellation and pregnancy of women having their first IVF treatment. Both in univariate and in multivariate analyses, psychological distress before and during treatment did not affect the chance of pregnancy.

In accordance with other studies on anxiety before and during first IVF treatment, we did not find an impact of baseline psychological factors or procedural anxiety on the pregnancy chance (Thierring *et al.,* 1993; Boivin and Takefman, 1995; Klonoff-cohen *et al.,* 2001; Emery *et al.,* 2003; Anderheim *et al.,* 2005; Smeenk *et al.,* 2005; de Klerk *et al.,* 2008). Influence of procedural stress in inductees before oocyte retrieval has been found only in small sample studies (Boivin Takefman, 1995; Facchinetti *et al.,* 1997; Galinelli *et al.,* 2001).
Former results from our own research group, showed that high baseline state anxiety and depression levels had a negative impact on the pregnancy chance of inductees (Smeenk *et al.,* 2001; Verhaak *et al.,* 2001), but this could not be confirmed later on (Smeenk *et al.,* 2005). In the latter study, the relation between anxiety and the pregnancy outcome was suggested with a lower baseline adrenaline and lower (nor)-adrenaline level at embryo transfer observed

in women who succeeded with a pregnancy. In the current study, this relation could not be confirmed with the procedural anxiety level measured before oocyte retrieval.

Surprisingly, higher women's age showed only a trend towards a lower pregnancy chance. All other biological factors studied (pregnancy history, cause and duration of subfertility), did not have an impact on the pregnancy rate. These factors have been shown to be of importance in large prospective studies (Templeton *et al.,* 1996; Lintsen *et al.,* 2007). Despite participation of a fairly large number of women in this study, the number was probably not high enough to reach significance in the prediction of pregnancy.

We showed that psychological factors were not associated with the cancellation rate. In daily practice, the most important reason for cancellation will be medical: imminent ovarian hyper stimulation, or in contrast, poor ovarian response. However, this was not reflected in a difference of biological characteristics between cancelled and non-cancelled women. The only factor predicting cancellation was a longer duration of subfertility.

We compared the baseline state anxiety and depression levels of women that completed a questionnaire pretreatment with the anxiety and depression scores of the Dutch Community norms and found the levels of our participants within the normal range. This is in accordance with the systematic review of Verhaak *et al.* (2007) in which the investigation of the emotional adjustment before the start of IVF treatment over the last 25 years is reviewed: the depression level of IVF patients was similar compared to the norm groups, but the pretreatment state anxiety scores differed considerably for patient groups as well as for norm groups. This difference in norm is partly explicable by cultural differences, but the difference in patient approach might be of even greater influence of the patient's emotional response.

We had access to the complete database of all eligible new patients and 70% participated, but selection bias of participants cannot be fully ruled out. Perhaps nervous women were not asked, or maybe women with high distress levels refused to participate. As far as biological patient characteristics are concerned, there were no differences between participants and non-participants, except for a longer duration of subfertility for inductees in the non-participating group, which we cannot explain.

We regret that lifestyle factors as smoking, overweight, caffeine and alcohol intake were not studied. Although of unarguable influence in IVF treatment and in fertility in general (Sharpe and Franks, 2002; Klonoff-Cohen, 2005; Lintsen *et al.,* 2005), the complexity of research, where lifestyle factors are understood as mediators in the relationship between distress and fertility, requires a different intention of study (Verhaak and Hammer Burns, 2006).

The emotional impact of an IVF treatment should not be underestimated, but we agree with Boivin *et al.* (1995) and Verhaak *et al.* (2007), that high expectations of the first treatment after adaptation to the subfertility problem after several years, will positively influence the

emotional disposition. On the other hand, after unsuccessful IVF treatment, 20% of women, showed subclinical forms of anxiety and/or depression (Verhaak *et al.,* 2005). We therefore do recommend research in the field of prediction (Verhaak *et al.,* 2006), and of counselling and therapy of women who are susceptible to, or have developed, emotional problems after unsuccessful IVF treatment.

In summary, in our large prospective study on psychological distress and IVF, we did not find an influence of anxiety and depression on the IVF cancellation rates or pregnancy rates. The small confidential intervals in the multivariate analyses implicate accurate findings. The coherence between psychological factors and IVF outcome is probably more complex and cannot be solved without the research of mediating factors as lifestyle and sexual behaviour. Large prospective studies on psychological and contributory factors are necessary to reveal more information about the interrelationship between emotions and fertility.

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Chapter | 8

Who is at risk for emotional problems and how do you know?

Screening of women going for IVF treatment at risk for emotional problems

8

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Abstract

Background: Fertility problems are accompanied by a lot of emotional distress, resulting in a considerable part of female patients showing severe maladjustment after artificial reproductive treatment. This interferes with their daily life, in addition, emotional distress has shown to be related to dropout of treatment and deterioration of health behavior. Early identification of women at risk enables the provision of timely psychosocial support and gives the opportunity of focusing psychosocial resources on those who need it most. This study investigated the psychometric characteristics of a screening tool SCREENIVF to identify women at risk for emotional problems in an early stage in the treatment.

Methods: Risk factors for emotional maladjustment were identified in a previous study and incorporated in SCREENIVF which consists of 32 items on general and infertility specific psychological factors. Two hundred and seventy nine women in their first IVF treatment cycle finished SCREENIVF at pretreatment and three to four weeks after the pregnancy test. Regression analyses were performed to investigate the predictive value of SCREENIVF, sensitivity and specificity as well as likelihood ratio's were described .

Results: SCREENIVF successfully identified 75% of the patients as at risk or not at risk. The negative predictive value was high: 89%. The positive predictive value was low (48% in the total sample and 56% after unsuccessful treatment). Sensitivity was 69%, Specificity was 77%.

Conclusions: For its use as a first screening for emotional problems, SCREENIVF is an acceptable instrument to identify women at risk. These women could be offered more detailed diagnostics e.g. in a diagnostic interview to further investigate to what extent they could benefit from psychological treatment. In addition, physicians can anticipate on this risk profile when communicating with these patients.

Introduction

The importance of paying attention to emotional outcomes of infertility and its treatment is increasingly recognized. This is partly stimulated by the increasing incidence of fertility treatment, in combination with a considerable part of the women who still does not succeed in achieving a pregnancy. The emotional burden of IVF is well documented (for reviews see Stanton & Dunkel-Schetter 1991; Greil 1997; Verhaak *et al.* 2007). It is a stressful emotional experience that could interfere with its outcome. Most couples adjust emotionally well to unsuccessful treatment. They experience emotional distress in terms of normal feelings of vulnerability, fear and grief. However, a considerable part shows disabling emotional problems such as anxiety and depression. Women seem more vulnerable than men to develop emotional problems as the result of IVF, in addition, unsuccessful treatment is an important risk factor for emotional maladjustment.

The emotional maladjustment could negatively contribute to the outcome of IVF. There is much debate about the direct relationship between psychological factors and the outcome of IVF. Some studies show a direct relationship between emotional stress and the outcome of IVF (Demyttenaere *et al*., 1992, Thiering *et al*., 1993, Klonoff-Cohen *et al*., 2001, Smeenk *et al*., 2001, Verhaak *et al*., 2001, Eugster *et al*., 2004, Boivin and Schmidt 2005). Others, however, found no relationship (Lintsen et al. 2009). Consequently, as yet there is not enough empirical evidence to justify psychological treatment for patients to improve their chance to get pregnant. More recently, the indirect impact of psychological factors on the outcome is more recognized by its role as mediator in the relationship between biological parameters and outcome of fertility treatment. Psychological factors have shown to be related to prematurely drop out of treatment by patients indicating emotional strains as important reason to prematurely stop treatment (Smeenk *et al.,* 2004, Olivius *et al.,* 2004, Verberg *et al*., 2008). Psychological factors also contribute to health behavior such as eating habits and smoking (Rollnick 1999). In addition, psychological factors in terms of prenatal maternal stress are negatively related to the outcome of pregnancy and subsequent health of children. This is well documented in spontaneous pregnancies (e.g. Bellinger *et al.,* 2008, Lazinsksi *et al.,* 2008; Beydoun *et al.,* 2008; Marcus 2009; Wisner *et al.,* 2009). From clinical point of view, it would be important to be able to identify women with an vulnerability for emotional problems in time, before starting treatment, enabling clinicians to offer them psychosocial care if needed, and to anticipate on this emotional vulnerability in their consultations. This could facilitate patients emotional adjustment to the treatment and its outcome, and probably contribute to more favorable health behavior and less drop out of treatment . Most physicians judge patients vulnerability for emotional problems on gut feelings. Studies in other patients samples indicate health care professionals difficulties in identifying those patients vulnerable for emotional problems. They correctly identified only 25% of the patients (Glazebrook *et al.,* 2003).

An adequate judgment of the need for psychological treatment is also important from patients point of view. Individual patients have difficulties in matching their own levels of distress, their perceptions of the merits of psychosocial support and its availability (Boivin *et al.,* 1999).

Studies into the effect of psychosocial interventions on distress levels of patients with fertility problems revealed contradictory results (For review see Boivin 2003; Connolly *et al.,* 1993; De Klerk *et al.,* 2008; Emery *et al.,* 2003). This is partly attributed to the heterogeneity of the patient groups (Wischmann 2008). One important issue is that the majority of patients with fertility problems suffer from their inability to get pregnant, but cope effectively with this emotional burden indicated by their satisfactory emotional adjustment (Verhaak *et al.,* 2005a; Verhaak *et al.,* 2005b). Patients who are already able to adjust well to the stressor of infertility are not likely to benefit much from additional psychosocial support. Moreover, it should be questioned if scarce availability of psychosocial professionals has to be offered to patients who are already well adjusted. It seems more reasonable to focus psychosocial treatment possibilities on those who need it most. This is in line with recommendations in several psychological intervention studies in infertility (Connolly *et al.,* 1992; De Klerk *et al.,* 2008). The challenge is not to improve emotional adjustment in all patients with fertility problems, but to identify those with (the risk of) serious adjustment problems in time, and to provide them psychosocial treatment, tailored to their individual vulnerabilities.

In the field of behavioral medicine, several studies have been carried out into risk factors for emotional maladjustment to various medical conditions. These studies are based on stress vulnerability models identifying existing distress levels, personality characteristics, coping, and social support as risk factors (Lazarus & Folkman 1984; Cohen & Wills, 1985; Clark *et al.,* 1994; Holahan *et al.,* 1996; Beck & Clark, 1997; Alloy *et al.,* 1999). The few prospective studies on risk factors for emotional problems in patients with fertility problems have found support for the importance of these factors (Terry & Hynes 1998; Schmidt *et al.,* 2005; Verhaak *et al.,* 2005a; Verhaak *et al.,* 2007; Cousineau & Domar, 2007). In our centre, a longitudinal prospective study identified pre treatment distress in terms of anxiety and depression, as well as strong focus on the child wish, less acceptance of the fertility problems and lack of perceived social support as risk factors for emotional problems after unsuccessful IVF in women. The study also indicated women as most severely emotionally affected by threatening infertility (Verhaak *et al.,* 2001). Accordingly, the identification of these risk factors resulted in the development of a short screening tool SCREENIVF which is aimed to identify women at risk for emotional maladjustment before the start of their IVF treatment. In this study, we investigated the validity of SCREENIVF in women. We investigated to what extend SCREENIVF, administered before the start of the first treatment cycle showed a predictive value for the emotional adjustment of women after this cycle in a large sample recruited from different fertility centers.

Materials and Methods

Design and subjects

Seven IVF clinics in the Netherlands participated into the study which was part of a larger study into the prediction of pregnancy with IVF or ICSI treatment performed in 2002-2004 (Lintsen *et al.,* 2007). Women with an indication for IVF or ICSI treatment according to the IVF guideline formulated by the Dutch Society for Obstetrics and Gynaecology (NVOG, IVF guideline no 9, 1998, www.nvog.nl), and starting first treatment, were eligible to participate in the study. For this study, they were asked to complete two short questionnaire: one was administered before the start of the treatment (T1), the other one three weeks after the pregnancy test (T2). The inclusion period covered 12 months per clinic. Exclusion criteria were inadequate apprehension of the Dutch language and use of donor gametes. The IVF outcome data and the fertility specific background variables as pregnancy history, duration and cause of sub fertility of all women participating in this study were registered in the national cohort study. The psychological dataset was matched with the IVF dataset of the 7 participating hospitals.

The ethical committees of the participating clinics gave approval for the study.

Distress measures

SCREENIVF was based on the results of our previous prospective study into the prediction of the emotional response to unsuccessful IVF treatment (Verhaak *et al.,* 2005a and Verhaak *et al.,* 2005b). This study revealed five risk factors: (1) pre treatment anxiety and (2) pre treatment depression, cognitive coping in terms of (3) helplessness and (4) less acceptance regarding fertility problems and (5) a lack of social support as risk factors for increased emotional problems. A short questionnaire was developed. It consisted of the scales assessing these five risk factors based on the previous study. This resulted in a 31 item questionnaire consisting of 10 items assessing state anxiety, 7 items assessing depression, 6 items assessing helplessness, 6 items assessing lack of acceptance and 5 items assessing perceived social support. The items assessing anxiety were based on a short version of Spielberger State and Trait Anxiety Inventory (Spielberger 1983, Van der Ploeg 2000) used in the IRGL (Invloed van Reuma of Gezondheid en Leefwijze; impact of rheumatoid arthritis on health and daily activities). The depression items were the 7 items of the short Beck Depression Inventory version for patients of general practitioners (Beck *et al.*,1997). The items on helplessness regarding fertility problems and acceptance of fertility were from the Illness Cognition Questionnaire for IVF patients (Evers *et al.,* 2001; Verhaak *et al.,* 2005b). Perceived social support was assessed by 5 items derived from the Inventory of Social involvement (Van Dam Baggen & Kraaimaat 1992). The assessments of anxiety, depression and perceived social support are based on generic instruments, the assessment of cognitive coping is based on a fertility

specific instrument. The different scales showed excellent reliability: anxiety alpha=.88; depression alpha =.82; helplessness alpha=.87; acceptance alpha=.92 and social support alpha=.89. The items of the helplessness, acceptance and social support scales of SCREENIVF are presented in the appendix, the items of anxiety can be found in Van Dam Baggen and Kraaimaat (1992), the depression items could be found following Beck et al. (1997).
SCREENIVF was handed out after pre-treatment information and instruction on self injection of the medication. Patients were asked to administer the follow up assessment three to four weeks after the pregnancy test. Emotional adjustment after the first treatment cycle was assessed in terms of anxiety and depression after the pregnancy test of the first treatment cycle. For the follow up assessment, the anxiety and depression scales of SCREENIVF were administered (Beck *et al.,* 1997; Van der Ploeg 2000). The follow up score consisted in continue scores on anxiety and depression. Additionally, the same cut off scores as in pre treatment assessment were used to indicate yes or no clinical relevant problems concerning anxiety and or depression. This resulted in a dichotomous variable: yes or no clinical problems at post treatment. Clinical problems at post treatment was defined as showing scores above the cut off for anxiety and/ or depression. The moments of assessment are presented in Table I.

Table I Assessments at different moments of measurement

Risk factors	Questionnaires	T1 pre treatment (SCREENIVF)	T2 post treatment
Anxiety	STAI short version: 10 items	X	X
Depression	BDI short version 7 items	X	X
Helplessness	Scale ICQ 6 items	X	
Acceptance	Scale ICQ 6 items	X	
Social support	5 items	X	

Patients were defined as at risk when their scores on one of the five risk factors showed clinical relevant problems. The cut off of the depression scale was 4 or higher. This is in line with the cut off presented in other studies (Beck *et al.,* 1997). The cut off for the short version of the STAI was based on scores of one standard deviation above the mean in a Dutch norm group consisting of women: score 24 and above. For the scores of helplessness, acceptance and social support, no norm scores were available. The cut off scores were based on one standard deviation above the mean scores of IVF-patients in a previous study (Verhaak et al. 2005a) resulting in a cut off of 14 and above for helplessness, 11 and less for acceptance and 15 and less for social support. Accordingly, SCREENIVF resulted in a dichotomous scores on each of the five risk factors: score 0 if the patient scored below the cut off, and score 1 when

scoring above or equal as the cut off score. The score range on SCREENIVF was 0 to 5: 0 indicating no risk factors and 5 indicating 5 risk factors.

Data analyses

In order to assess to what extend the five scales of SCREENIVF, administered at T1 could predict anxiety and depression after one treatment cycle, two multiple regression analyses were performed with anxiety and depression post treatment (T2) as dependent variable. In the first step, baseline levels of the dependent variable (anxiety or depression) were entered, in the second step the other predictors (baseline anxiety or depression; helplessness, acceptance, social support) were entered.

In addition, the predictive value of the screening tool was assessed by investigating to what extend SCREENIVF could predict yes or no clinical emotional problems at post treatment. This was assessed using likelihood ratios assessing the probability that a patient with clinical problems at T2 is indeed identified as at risk at T1, divided by the probability that a patient without clinical problems was identified as at risk at T1. Clinical emotional problems at post treatment (T2) were defined as a dichotomous variable indicating showing yes or no clinical relevant anxiety and or depression at post treatment (T2). Likelihood ratios of 1-2 indicate a minimal increase in likelihood of the disease by using the test, 2-5 is a small increase, 5-10 a moderate increase and more than 10 a large increase (Ebell, 1999).
In addition, sensitivity (the probability of having a positive screening result among patients with clinical emotional problems), specificity (the probability of having a negative screening result among patients without clinical emotional problems), positive predictive value (the probability of having clinical emotional problems among patients with a positive screening result), and negative predictive value (the probability of having no clinical emotional problems among patients with a negative screening result) were computed.

Results

555 Women in seven centers agreed to participate, 279 (50%) completed both T1 and T2 questionnaires. Pregnancy rate as well as baseline anxiety, depression, cognitions regarding infertility and social support did not differ between women who completed both questionnaires and those who did not. Thirty three percent of the treatment cycles resulted in an ongoing pregnancy confirmed by an ultrasound in week seven.

Table II shows that 34% of the patients showed clinical relevant problems at T1. In the table, the mean scores on anxiety, depression, helplessness, acceptance and social support at T1 as well as the percentage of patients showing clinical relevant problems on these risk factors is

Table II Different risk factors at T1: mean scores and percentage of women scoring at risk

	Mean score (SD) T1	% women above cut off
T1 At risk		34%
T1 Anxiety	17.3 (4.8)	10
T1 Depression	1.3 (2.4)	11
T1 Helplessness	10.9 (3.7)	16
T1 Acceptance	15.8 (4.2)	16
T1 Social support	18.3 (2.8)	16

also indicated. In addition, it shows the percentage of patients showing clinical emotional problems. At post treatment (T2), 24% of the women showed clinical relevant emotional problems.

Predictive value of the screening tool

Two regression analyses were performed to assess the predictive value of the screening tool administered at T1 for respectively anxiety and depression at T2. In Table III, R^2 and R^2 change are indicated for the various regression analyses. The findings show that SCREENIVF significantly predicted post treatment anxiety and depression. In all analyses, the cognitions regarding fertility problems and social support, next to baseline anxiety or depression, added

Table III Regression coefficients and R^2 change for prediction of anxiety and depression by two regression analyses

Total sample	R^2	R^2 change	Significance
Regression analysis 1			
Anxiety T1	.37		< .000
Cognitions regarding fertility problems and Social support	.41	.04	.008
Regression analysis 2			
Depression T1	.23		<.000
Cognitions regarding fertility problems and Social support	.33	.10	<.000

significantly to the explained variance. Baseline anxiety explained 37% of the variance in post treatment anxiety, the other risk factors added 4% in explained variance. Baseline depression explained 23% of the variance in post treatment depression, the other risk factors added 10% in explained variance.

Sensitivity and specificity

Performance of SCREENIVF in detecting post treatment anxiety and depression is indicated in Table IV.

SCREENIVF identified 34% of the women (95 out of 279) as at risk at pre treatment (T1). The sensitivity was 69%, the specificity 77%. This means that SCREENIVF identified 69% of the patients as at risk, who indeed showed problems at T2 (46 out of 67). In addition, 77% of the patients without problems at T2, were indeed not identified as at risk by SCREENIVF at T1 (163 out of 212). The positive predictive value was 48, the negative predictive value was 89, indicating that SCREENIVF better identified patients without clinical problems, than patients with clinical problems: relatively less patients who were identified as not at risk (21 out of 184), still developed problems post treatment, however, relatively more women who were identified as at risk, showed no emotional problems at T2 (49 out of 95). The overall efficiency of SCREENIVF was 75%: 46 patients were correctly identifies as at risk and 163 were correctly identified as not at risk. This means that SCREENIVF was able to identify 209 out of 279 patients correctly.

Table IV Comparison between screened at risk at T1 with clinical problems at T2. Numbers in bold indicate numbers of patients correctly identified by SCREENIVF.

N=279	**Clinical problems after IVF (T2)**		
SCREENIVF = at risk (T1)	Yes	no	Total
YES	**46**	49	95
NO	21	**163**	184
Total	67	212	279

Table V shows the differences in proportion of clinical problems after treatment in patients who were and those who were not identified as at risk by SCREENIVF. In the bottom row it is shown that 48.4 % of patients who were identified as at risk when entering treatment (T1) showed clinical emotional problems after treatment (T2) compared to 11.4% in patients not identified as at risk (Likelihood ratio 3.0). The top row indicate that patients showing anxiety

Table V Differences in % post treatment clinical problems by pre treatment assessment and likelihood ratios

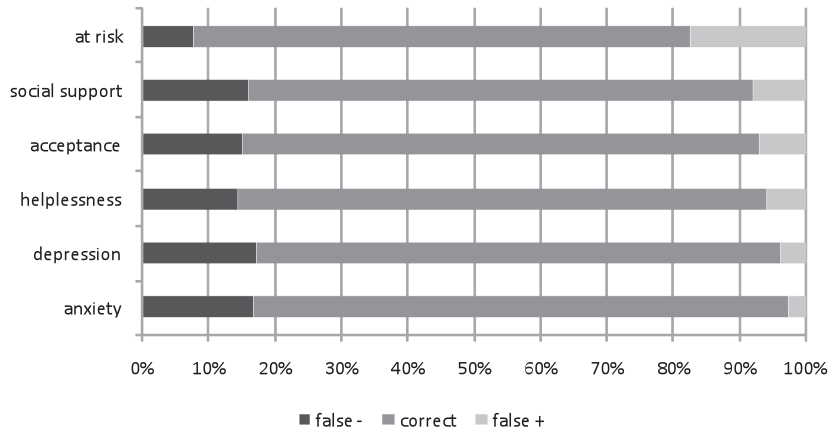
Risk factor at pre treatment (T1)	% clinical problems at post treatment (T2)	likelihood ratio
Anxious Yes No	 71.4 18.6	7.5
Depressed Yes no	 63.3 19.0	5.7
Helplessness Yes No	 61.4 16.9	5.0
Less acceptance Yes no	 55.6 17.9	4.1
Less social support Yes No	 48.9 19.1	3.0
1 or more risk factors Yes No	 48.4 11.4	3.0

at pre treatment had greatest chance showing clinical problems at post treatment: 71.4% of the patients with clinical anxiety at pre treatment (T1) showed clinical problems at T2 compared to 18.6 % of the patients without pre treatment anxiety (likelihood ratio 7.5).
Figure 1 indicates the predictive value of the risk factors, assessed at T1 for emotional problems at T2. It indicated how many patients showed emotional problems at T2 after being screened as at risk on one of the indicated factors (correctly identified, middle grey part of the bar), it indicates how many patients were screened as not at risk, but who showed clinical problems at T2 (false negative, dark grey part of the bar), and how many patients were screened as at risk, but who showed no clinical problems at T2 (false positive, light grey part of the bar).

Discussion

In general, SCREENIVF performed as an acceptable screenings instrument to differentiate between women entering IVF treatment with lower and higher risk for emotional problems during and after an IVF treatment cycle. Likelihood ratio's indicated small improvement for identification of patients at risk by use of SCREENIVF, when focusing on specific risk factors, improvement was moderate for patients showing anxiety or depression at pretreatment.

Figure 1 Classification of IVF patients based on SCREENIVF compared to post treatment emotional problems



SCREENIVF can be used as a screening tool before the start of the treatment, but also after the first treatment cycle, going to a second one.

The performance of SCREENIVF should be interpreted against the purpose for which it is used. In clinical practice, SCREENIVF can be used as a screening tool to identify women with a risk profile for emotional problems. Physicians and nurses could anticipate on this risk profile to pay special attention to the emotional aspects of the treatment in patients at risk. For instance, pay special attention to these patients when giving instructions before treatment, ask them for need for an additional appointment when treatment progress is un satisfactory. In addition they could offer these patients a reference to a psychosocial professional who is able to investigate the possible need for psychosocial support for the individual patient. In that case, SCREENIVF is a first step in a triage for judging the need for additional psychosocial support for women entering IVF. The second step is the more thorough diagnostic investigation which could identify those who need additional psychosocial treatment (third step) and those who do not. Using SCREENIVF is an improvement from overall clinical practice of offering psychosocial support on face value by physicians or nurses, or on initiative of patients themselves. Such a triage is already recommended in other patient groups like patients with cancer (Carlson & Bultz, 2003; Thomas *et al.,* 2008), COPD (Vercoulen *et al.,* 2008).

Studies in other health care patient groups already indicated that identification of patients at risk for emotional problems is difficult for health care professionals. On average only 25% is identified correctly (Glazebrook *et al.,* 2003). Recently, the study of Volgsten *et al.,* (2008) showed that the majority of women who suffered from psychiatric morbidity, did not receive the support they needed . Entering these women in a strenuous treatment like IVF is accompanied by the risk of further deterioration of emotional wellbeing, especially in case of unsuccessful treatment.

This study only focused on women. The emotional impact of fertility problems in men is still insufficiently investigated. Many studies do not take men into account (Hynes et al., 1992; Lok et al., 2002; Verhaak et al., 2005; Visser et al., 1994). Several other studies showed a lower emotional impact of fertility problems in men compared to women (Lund et al., 2009; Newton et al., 1990; Slade et al., 1997; Verhaak et al., 2001). It is suggested that men seem to be affected differently by the stress of subfertiity than women, differently in a way that does not seem easily recognizable by standardized general psychological meassures. Specific assessment tools, measuring infertility related distress, will probably better identify the emotional impact of fertility problems in men. However, disease specific measures often lack informtaion about norms which makes interpretations of scores in relation to general emotional wellbeing difficult. This does not mean, however, that men should be left out of screening procedures. Men with clinical relevant emotional problems at the start of IVF will be more at risk for deterioration of their emotional health than others. However, the state of research into other predictors of emotional adjustment problems in men still does not provide sufficient information for the selection of the most important risk factors. This paper offers a recommendation for screening patients on emotional health before they start their IVF tratment. This recommendation includes both men and women. SCREENIVF provides a validated instrument that included only women. The next step is to include men too, in a study to investigate the predictive validity of SCREENIVF. SCREENIVF should not reveal a prerequisite for psychosocial support. The positive predictive value does not prove this. However, a screening tool such as SCREENIVF can provide patients information on their risk profile and could give them the feedback that they could benefit from additional psychosocial support. In optimal circumstances, this support could be given by a psychosocial professional within the team of reproductive medicine. However, physicians and nurses are able to, based on the risk profile of the patient, address the psychosocial issues of the treatment with the patient or to anticipate on possible negative effects of the emotional vulnerability of the patient on the treatment outcome.

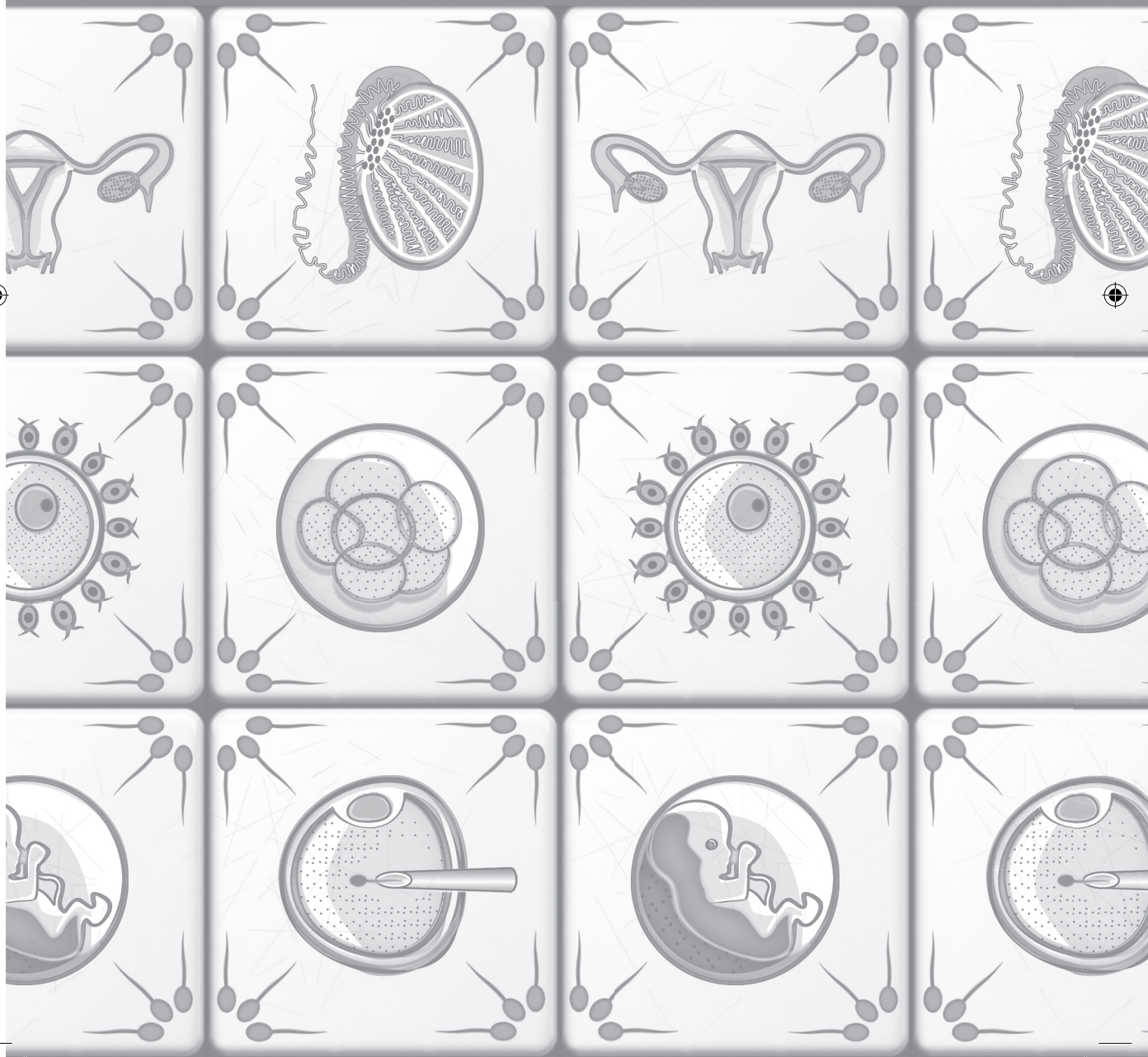
Another reason to avoid a positive screening result as prerequisite for referral for psychosocial support is the limited sensitivity. Still nearly one third of the women showing clinical emotional problems after IVF was not identified correctly. This gives the risk of deterioration

of emotional health in special cases such as threatening psychiatric morbidity or escalation of problems in intimate relationships. Sensible care for patients treated with IVF should take their emotional well being into account in order to be able to anticipate on possible risk factors for deterioration of the emotional condition as well as to integrate issues regarding emotional health in decision making regarding treatment.

In sum, patient care in infertility would improve by screening patients on psychosocial health when they enter treatment and when they pass different kinds of treatment. It provides evidence for the gut feeling of the clinician. In addition it offers both clinicians an patients to anticipate on emotional vulnerability of the patient and its possible negative effects on the course of the treatment.

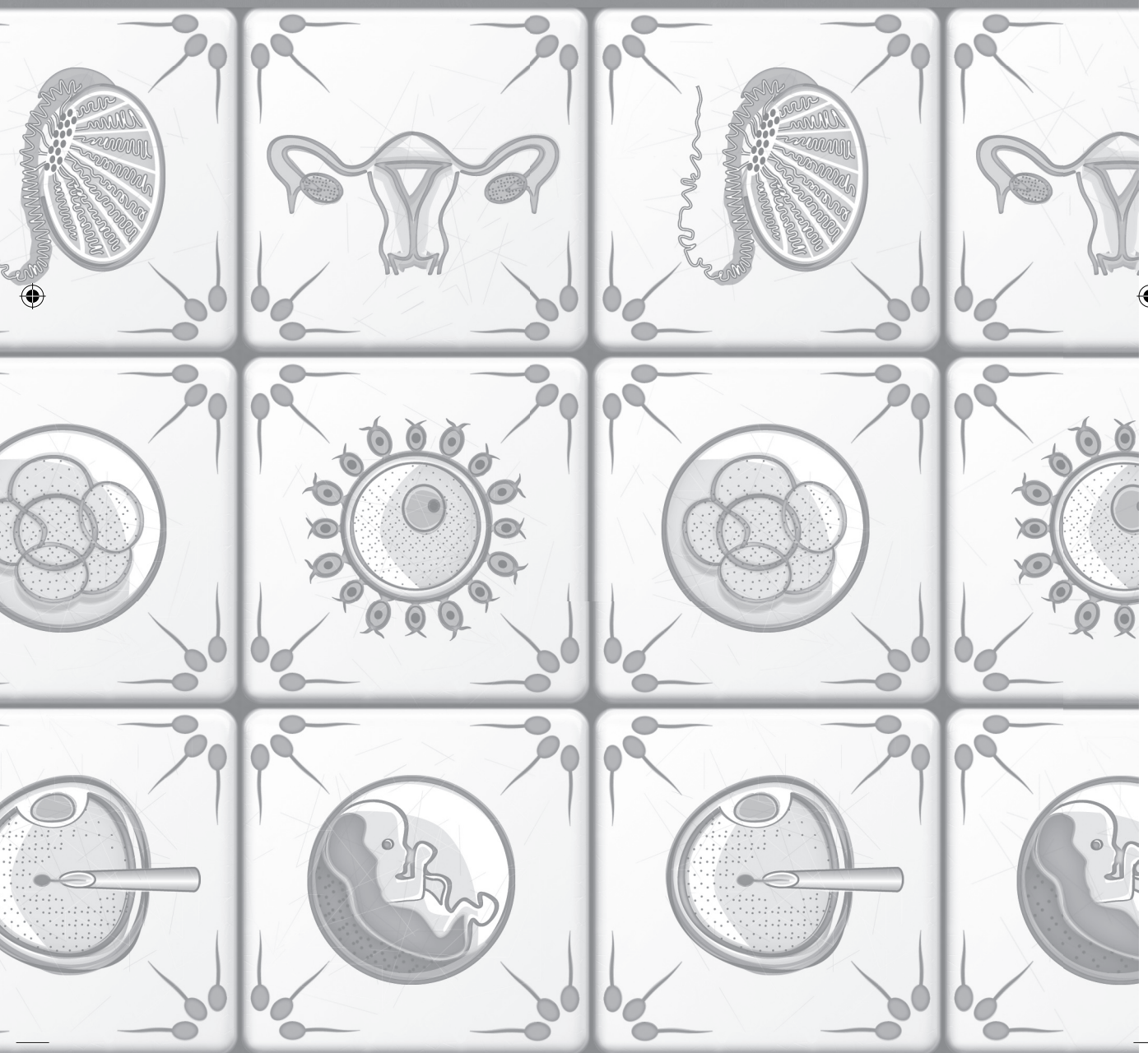
Appendix

Items of three scales SCREENIVF: helplessness, acceptance, social support
My infertility frequently makes me feel helpless
My infertility limits me in everything that is important to me
My infertility controls my life
Because of my infertility, I miss the things I like to do most
My infertility prevents me from doing what I would really like to do
My infertility makes me feel useless at times
I have learned to accept my infertility
I have learned to live with my infertility
I can accept my infertility well
I can cope effectively with my infertility
I think I can handle the problems related to my infertility even if they will not be solved
I can handle the problems related to my infertility
If I feel distressed, there is someone to help me
If I enjoy things, there is someone to share with
If I'm in pain, there is someone supporting me
If I'm sad, there is someone to share with
If I need help with a small job I cannot do alone, there is someone helping me



Part | III

Costs



Chapter | 9

Absence from work and emotional stress in women undergoing IVF or ICSI.

An analysis of IVF-related absence from work in women and the contribution of general and emotional factors

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Abstract

Objective: To assess productivity losses due to absence from work during IVF/ICSI treatment and to describe the pattern of IVF-related absence from work. Additionally, the influence of general and psychological variables on IVF-related absence from work was analysed.

Design: Prospective cohort study.

Setting: Eight IVF hospitals participated in the study.

Sample: Women undergoing their first treatment with IVF/ICSI.

Methods: The HLQ was used to estimate the costs of IVF-related absence from work (n=384). Diaries were used to collect back ground information and reasons for IVF-related absence. Psychological data were derived using the STAI, BDI-PC, Inventory Social Relations and the Illness Cognition Questionnaire. Regression analyses were performed using two models, one without and one model with psychological data, to assess the impact of the different variables on IVF-related absence from work.

Main outcome measure: IVF-related absence from work and the costs of productivity losses due to IVF/ICSI per treatment.

Results: Overall absence from work during IVF/ICSI treatment was on average 33 hours, of which 23 hours were attributed to IVF/ICSI. Costs of productivity losses due to IVF/ICSI were € 596 per woman. Significant predictors of IVF-related absence from work were the number of hours of paid work, age and self-reported physical and/or emotional problems due to IVF treatment.

Conclusions: Women experiencing emotional complaints and women with physical complaints due to IVF/ICSI reported significantly more IVF-related absence from work.

Introduction

The introduction of in vitro fertilisation (IVF) was a breakthrough in bypassing barriers to fertilisation in couples failing to achieve a spontaneous pregnancy. Intracytoplasmic sperm injection (ICSI), a variant of IVF, was added in 1992 for couples suffering from severe male infertility. Nowadays IVF and ICSI are frequently adopted interventions. In 2000, about 2% of all newborns in the Netherlands were born after IVF or ICSI and this percentage continues to increase (Kremer *et al.,* 2002).

The (direct) medical costs of IVF and ICSI treatment are high (Collins *et al.,* 2002), but little is known about the indirect costs. Indirect costs originate from sick leave (hereafter called absence from work) due to health-related problems, which may result in productivity losses. The international literature reports that the costs of productivity losses related to IVF are about 10% or more of the total costs per treatment cycle (Neumann *et al.,* 1994; Stern *et al.,* 1995; Fiddelers *et al.,* 2006). However, in most of these studies, it was unclear whether costs of productivity losses were based on empirical data on absence from work. The most recent study was performed in the Netherlands and presented cost estimates based on actual data on absence from work in both women and their partners during a four week IVF treatment period (two weeks before and two weeks after the embryo transfer) (Fiddelers *et al.,* 2006). The average costs of productivity losses related to IVF treatment were approximately € 456 per treatment cycle per couple. The authors stated that the costs of productivity losses were mainly due to absence from work of the women whereas their partners were more likely to take days off. However, an IVF/ICSI treatment cycle generally covers a longer period than 4 weeks. In a national Dutch costing study, the period from pituitary down regulation, the so-called "long protocol", followed by ovarian hyper stimulation up to the embryo transfer alone, was found to average already some four weeks (Bouwman *et al.,* 2008). Consequently, productivity losses due to IVF/ICSI treatment cycle may appear over a longer period.

Besides the number and costs of absence from work in IVF/ICSI treated women, information on the predictors of absence from work in this group is limited. Both physical and emotional complaints due to the treatment may contribute to absence from work. Emotional distress in particular may lead to an increase of absence from work, as the emotional impact of fertility treatment is commonly considered to be even more strenuous than the physical impact of the treatment (Kopitzke *et al.,* 1991). Studies have indicated that, next to pre treatment anxiety and depression, lack of social support and appraisals of helplessness with fertility problems are risk factors for emotional problems (Verhaak *et al.,* 2005).

This study aimed to describe the number and the pattern of absence from work during an average IVF/ICSI treatment cycle and to estimate the costs of productivity losses in women

with paid work. Additionally, we analysed the extent to which general and emotional factors had contributed to absence from work.

Materials and Methods

Data and methods

From January 2002 through March 2005 a national cohort study was performed in the Netherlands to assess the cost-effectiveness of IVF/ICSI in women undergoing IVF/ICSI (n=9016). Alongside this study, data on absence from work were collected in 8 IVF centres and transport clinics (from a total of 31 centres and clinics), thus presenting a representative sub sample of the women who participated in the national study. A total of 660 women were asked to fill in daily diaries during their first treatment cycle starting at the first day of gonadotrophin-releasing agonist injections (defined as the start of treatment) until 10 weeks thereafter.

The 10-week follow-up period generally covered an average treatment period including the post treatment evaluation (e.g. 4 weeks preceding the embryo transfer and 6 weeks after the embryo transfer). For the measurement of absence from work, the Health and Labour Questionnaire (HLQ) was used, which is a validated questionnaire that differentiates between different causes for health-related absences from work (Hakkaart-van Roijen *et al.,* 1999). For this study, we asked the respondents to distinguish between absence from work related to IVF/ICSI (hereafter called IVF-related absence) and absence due to other health-related problems. In addition, we collected data on general characteristics of the respondents, e.g. age, educational level and work status. Information about work status comprised questions about the number of paid work per week (e.g. number of days per week and number of hours per day of paid work). Furthermore, the women were asked to report the *main* reason for IVF-related absence from work during this period: 1) physical problems, 2) emotional problems, 3) both or 4) hospital visits.

Additionally, data on psychological factors were derived. For the measurement of pre treatment anxiety and depression, the translated short version of the Spielberger State and Trait Anxiety Inventory (STAI) (van der Ploeg *et al.,* 2000; Spielberger 1983), and the short version of the Beck Depression Inventory for Primary Care (BDI-PC) (Beck *et al.,* 1997) were used. Both questionnaires are validated instruments and provide an indication of the presence of general emotional distress in the patient. Factors that may contribute to emotional distress, e.g. perceived social support and appraisals regarding fertility problems, were assessed by the Inventory Social Relations (van Dam- Baggen *et al.,* 1992) and the Illness

Cognition Questionnaire, which were adjusted to the infertile population (Verhaak *et al.,* 2005; Evers *et al.,* 2001). Appraisals were defined as the evaluation of fertility problems in terms of acceptance of possible infertility and helplessness towards infertility and the degree of feelings of benefit from IVF/ICSI treatment.

Data analyses

Data of women with paid work were used for the analyses. Descriptive analyses were performed on raw data and imputed data were used for inferential analyses. In order to account for missing data and the additional uncertainty this introduces, we used multiple imputation on data related to absence from work. This is a technique in which each missing value is replaced by simulated values (Rubin and Schenker 1991; Rubin 1987; Lavori *et al.,* 1995). Data on the number of days of absence from work of 26 % of the respondents were incomplete. As is often the case, the number of missing values increased with the duration of the follow-up period. For the fractions of missing data (7%) in this study 10 simulations were found to be sufficient to stabilise the outcomes in terms of the SE for all analyses. The resulting imputed versions of the complete data were analysed separately by standard complete-data methods. These results were then combined to produce a single result that includes uncertainty due to missing data (Rubin 1996; Schafer 1997). We used SAS Proc MI for the imputations, with the Monte Carlo Markov Chain (MCMC) approach. Student's t-tests were used to analyse differences in absence from work between subgroups. Cross-sectional relations were explored using the Pearson correlation coefficient or Spearman's rho (in case of categoral variables).

In order to assess the impact of general and emotional factors on IVF-related absence from work, two models were constructed, one of which included general variables (hours of paid work, age and educational level) combined with the self-reported main reason for absence from work. This was called the general model. In the second model, general variables were combined with emotional factors. This model was called the emotional model. Anxiety and depression were summarized to a composite score called 'general distress' by using standardised Z-scores.

On the basis of regression analyses the prognostic value on IVF-related absence from work of each model was assessed. Statistical significance was defined at p=0.05.

Calculation of productivity losses

The costs of productivity losses due to absence from work were calculated in accordance with the Dutch guideline for economic evaluations in health care (Oostenbrink *et al.,* 2004). Hourly costs of productivity losses, based on national figures, differentiated to age of the women were taken from the guideline and adjusted to 2006 prices using national labour index figures (Statistics Netherlands CBS, http://statline.cbs.nl). Previous research has shown that a reduction of labour time due to absence from work causes a less than proportional

decrease of work activity (Koopmanschap *et al.,* 1995). Therefore the guideline recommends applying an elasticity of labour time and productivity of 0.8 for the calculation of the cost of productivity losses. Thus costs estimates were calculated on the basis of the hourly costs of productivity losses multiplied by 0.8 times the number of hours of absence from work. All costs are presented in 2006 euros.

Results

A total of 411 (62%) women returned the diaries, of whom 384 (93%) reported having a paid job. The characteristics of the respondents with a paid job and the results of the IVF/ICSI treatment cycles are presented in Table I.

Table I Characteristics of the women with paid work and results[a] of IVF/ICSI treatment (n=384)

		Mean (SD)	N (%)
Age (years)		32.4 (3.5)	
Paid work per week (hours)		28.3 (8.6)	
IVF/ICSI treatment results	Oocyte retrieval		371 (96.6)
	Embryo transfer		346 (90.1)
	Pregnancy rate		129 (31.3)
Educational level	Low		50 (13.7)
	Secondary		199 (52.5)
	High		132 (33.8)

[a] Results on the basis of one IVF/ICSI treatment per women during 10-week follow-up

Of all the women with paid work, 62% reported IVF-related absence from work. Overall, IVF-related absence from work averaged 23 hours (SD 37.3).

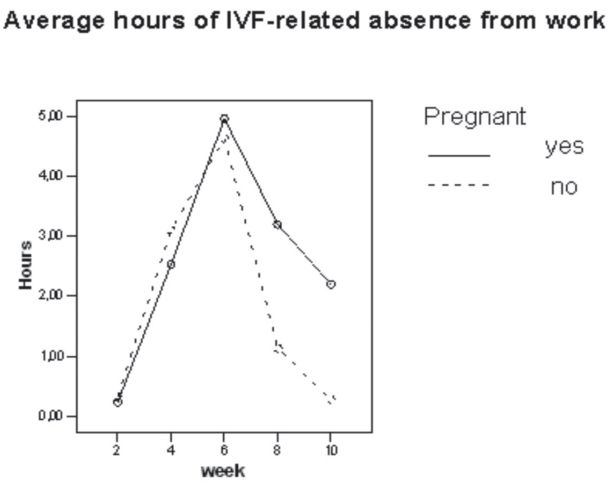
In Table II, the results on absence from work are presented of the women, grouped by the self-reported *main* reason of IVF-related absence from work. Over 50% of the women reporting IVF-related absence from work attributed the absence mainly to visiting the IVF centre. The volume of IVF-related absence from work in these women was relatively low compared to the women with physical and/or emotional problems. Over a quarter of the women reported that IVF-related absence was mainly caused by physical complaints and about 23% of the women reported that emotional problems (alone or combined with

Table II Absence from work (in hours) and costs of productivity losses (in 2006 euros) during IVF/ICSI treatment[a]

Main reason of IVF-related absence from work [b]	**Mean hours IVF- related absence from work (SD)**	**Mean costs IVF-related absence from work (SD)**	**Mean hours non-IVF- related absence from work (SD)**	**Mean costs non-IVF-related absence from work (SD)**	**Total costs absence from work (SD)**
Physical problems (27%)	42.0 (54.0)	1077 (1375)	18.0 (64.6)	491 (1783)	1568 (2060)
Emotional problems (6.1%)	40.8 (41.0)	1049 (1041)	12.8 (25.2)	345 (695)	1394 (1224)
Physical and emotional problems (16.6%)	40.7 (36.9)	1044 (938)	21.7 (55.4)	551 (1402)	1595 (1589)
Visits to the IVF centre (50.4%)	10.0 (17.0)	261 (458)	2.2. (10.8)	59 (296)	320 (541)
All women with paid work	**23 (37.3)**	**596 (955)**	**9.5 (40.0)**	**250 (1077)**	**845 (1417)**

[a] from the start of treatment (first day of gonadotropin analogue) until 10 weeks thereafter.
[b] 62% of all women with paid work reported IVF-related absence from work.

Figure 1 The pattern of IVF-related absence from work during 10 weeks following the start of treatment with gonadotrophin-releasing hormone injections



physical problems) were the main reason for IVF-related absence from work. The hours of IVF-related absence from work in women with physical and emotional problems (or both) were comparable.

The pattern of IVF-related absence represented the treatment course (see Figure 1). The number of hours of IVF-related absence steeply increased from 0.3 hour on average at the start of treatment to 7.2 hours in week 5 of the follow-up period, which generally coincided with the period in which the oocyte retrieval and the embryo transfer were performed. Next, IVF-related absence from work decreased rapidly from 4.7 hours in week 6 to 0.9 hours in week 10.

IVF-related absence from work at the end of the follow-up period was relatively higher in women who became pregnant compared to the women who did not get pregnant after the IVF/ICSI treatment. The difference was, on average, two hours in week 8, week 9 and in week 10, but this was not significant.

Absence from work due to other health related problems was reported by 19% of the women and amounted to 9.5 hours (SD 40.0) on average. Notably, both IVF-related absence from work and absence related to other health problems were highest among women who reported physical and emotional problems as the main reason for IVF-related absence. Overall, the average costs of productivity losses due to absence from work during the 10-week follow-up

period were € 845 (see Table II). About 68% of these costs were attributed to IVF/ICSI treatment, resulting in, on average, € 596 in costs of productivity losses per IVF/ICSI cycle started. By comparison, the average costs of productivity losses due to IVF-related absence from work in all women reporting physical or emotional problems or both as the main reason for IVF-related absence from work almost doubled to on average € 1063 per cycle.

T-tests revealed that the number of hours of IVF-related absence from work between women with different educational levels were not significantly different. A significant difference was found between women reporting IVF-related absence from work and those with no IVF-related absence concerning the hours of paid work. Women with no IVF-related absence worked on average 2.8 hours less per week (95% CI: 0.85 to 4.82). The average weekly hours of paid work were significantly higher among high-educated women (mean difference 4 hours; 95% CI: 2.5 to 5.9). Age of the women and IVF-related absence from work correlated significantly: the number of hours of absence decreased with increasing age of the women (rho = - 0.15; 95% CI: -0.25 to -0.04). Additionally, age and educational level correlated significantly (rho = 0.11; 95% CI: 0.01 to 0.21).

No correlation was found between the number of IVF-related absence and absence from work due to other health-related problems. Additionally, absence due to other health-related problems was not significantly correlated with the hours of paid work of the women or age of the women.

Regression analyses using the general model showed that the number of hours of paid work per week appeared a significant predictor of IVF-related absence from work (Table III). Additionally, women with a secondary education level reported significantly more IVF-related absence from work in comparison to more highly educated women. Finally, the self-reported reason for IVF related absence from work had a significant predictive value.

Women experiencing physical and/or emotional problems had, on average, 32 hours more IVF-related absence from work compared to the women who attributed absence from work primary to the hospital visits. The regression analyses resulted in a predictive value of 19.1 % (adjusted R square), meaning that the general model was able to explain approximately 19 % of the variances in IVF-related absence from work.

Pre treatment anxiety, helplessness, acceptance and to a lesser extent perceived social support correlated significantly, though moderately, with IVF-related absence from work. However, further analyses showed that all these factors correlated significantly with each other.

In the emotional model, as in the general model, the number of hours of paid work was a significant predictor of IVF-related absence from work. The predictive values of the emotional factors on IVF-related absence from work were limited and the only significant contribution was shown by acceptance of and feelings of benefit towards the fertility treatment. Regression analyses showed that the predictive value of the emotional model was 5.8% (adjusted R square).

Table III Two predictive models of IVF-related absence from work

General model Explanatory variable	Regression coefficient	Standard error	**Emotional model** Explanatory variable	Regression coefficient	Standard error
(Constant)	21.4	20.5	(Constant)	54.3	28.5
Hours of work	0.5[a]	0.2	Hours of work	0.5[a]	0.3
Age	-1.0	0.6	Age	-0.9	0.6
Lower education	14.6	8.3	Lower education	13.2	7.2
Secondary education	8.5[a]	4.2	Secondary education	7.4	4.5
Main reason of absence:			Acceptance	-1.6[a]	0.6
Physical problems	33.0[a]	4.6	Benefit	2.8[a]	1.4
Emotional problems	31.7[a]	8.6	Social support	-0.5	0.8
Physical & emotional problems	31.5[a]	5.5	General distress	0.4	1.5

[a] significant predictor of IVF related absence from work ($p < 0.05$).

Discussion

Overall absence from work during the 10-week follow-up of IVF/ICSI treatment among women with a paid job was on average 33 hours, of which 23 hours were attributed to IVF/ICSI treatment. Costs of productivity losses due to IVF/ICSI treatment were € 596 on average per cycle.
Overall, IVF-related absence from work was highest during the days around the oocyte retrieval and the embryo transfer. Both procedures involve relatively more contact time with the IVF-centre in comparison with the other visits. Above all, these procedures may go together with more physical and emotional stress.
The number of hours of paid work, the self-reported main reason for IVF related absence, and appraisals regarding infertility and infertility treatment were significant predictors of IVF-related absence from work. The influence of educational level of the women on IVF-related absence from work was less clear. On the basis of the results of the t-test in combination with the regression analyses, we assumed a trend of less IVF-related absence from work in more highly educated women. Probably, the non-significant difference within this study was due to the small sample size of the women with a lower educational attainment.

As far as we know, this is the first study to combine data on IVF-related absence from work with psychological data. Although most emotional data correlated significantly with IVF-related absence from work, the regression analyses showed that, especially, acceptance of infertility and perceived benefit of fertility treatment, which are both indicators of the ability of coping, had a predictive value on IVF-related absence from work.
Additionally, the regression analyses showed that the model that included data on emotional variables was less suitable in interpreting the variation in IVF-related absence from work among the women. Based on the general model it can be concluded that emotional problems and physical problems contribute equally to an increase of IVF-related absence from work.
Moreover, these two factors appear in approximately 50% of the women who reported IVF-related absence from work (e.g. 30% of all women).
IVF-related absence from work was higher in women who got pregnant, although the difference was not significant, compared to the hours of absence from work in women who did not become pregnant after the IVF/IVSI treatment. This difference may have been caused by pregnancy complications (e.g. bleeding, ectopic pregnancy or miscarriage).
Additionally, other medical parameters may have contributed to the variance in IVF-related absence from work during these periods. It would be interesting to assess the influence of these factors in future studies.
IVF-related absence from work and absence due to other health-related problems were not correlated. Despite this, both IVF-related absence and absence related to other problems seemed higher in women viewing physical and/or emotional problems as the main reason

for their IVF-related absence from work. Possibly, the distinction between IVF and non-IVF related absence from work is less clear for women with these problems.
Thirty-eight percent of the women reported no IVF-related absence from work. Additionally, the number of hours of IVF-related absence from work was relatively low in the women who reported visits to the IVF centre as the main reason for absence from work in comparison with the average number of hospital visits (6) during a complete IVF/ICVSI cycle.
No correlation was found between the number of hours of paid work and absence from work due to non-IVF related health problems. Nor were age of the women and absence due to other health related problems correlated, contrary to the correlations found between these factors and IVF-related absence from work.

The response rate of the diaries was 62%, which seems comparable with response rates in other studies (Slade *et al.,* 1997; Newton *et al.,* 1990; Hammarberg *et al.,* 2001) The response rate is relatively satisfactory, taking into account the effort women had to spend in completing the daily assessments during a period of 10 weeks. Additionally, as this was a multicentre study, the response rates may have been lower than those from single studies.

Results of the national study showed that during the first IVF/ICSI cycle 90% of the women starting IVF/ICSI with gonadotrophin analogues injections proceeded to the oocyte retrieval. In approximately 73.5% of the women an embryo transfer was performed (Bouwmans *et al.,* 2008). However, the pregnancy rates were comparable. Given the relatively high percentages of oocyte retrievals and embryo transfers in the women who participated in our study, non-response was probably partial caused by women with incomplete treatment cycles. It is not clear how this may have biased our results.

Seven percent of the responders were women without paid work. In the study of Fiddelers *et al,* it was reported that 11% of the women were unemployed. Probably, women without paid work were less likely to return the diary.
Given the course of IVF-related absence from work, we assume that the 10-week follow up period was representative of absence from work related to IVF/ICSI treatment. Our findings were in line with the results presented by Fiddelers *et al.* (2006). However, a detailed comparison was not possible, since data on absence from work were not presented and the follow-up period differed.

Our study used data collected in women during their first IVF/ICSI cycle. Emotional distress, and therefore absence from work, may be higher in women undergoing their second or third treatment cycle. More research is necessary to assess the impact of the number of treatment cycles on IVF-related absence from work. This study was performed in a large group of

women; hence the results on absence from work and costs of productivity losses are representative for Dutch women with paid work undergoing IVF/ICSI.

In summary, both women who experienced emotional and women with physical complaints due to IVF/ICSI reported significantly more IVF-related absence from work. The absence especially concentrated around the period of the oocyte retrieval and the embryo transfer. Future research should be aimed at possible ways of reducing the physical and emotional impact on women of IVF/ICSI during the treatment.

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Chapter | 10

A detailed cost analysis of in vitro fertilization and intracytoplasmic sperm injection treatment

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Abstract

Objective: To provide detailed information about costs of in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) treatment stages and to estimate the costs per IVF and ICSI cycle and ongoing pregnancy.

Design: Descriptive micro-costing study.

Setting: Four Dutch IVF centers.

Patient(s): Women undergoing their first treatment cycle with IVF or ICSI.

Intervention(s): IVF or ICSI.

Main outcome measure(s): Costs per treatment stage, costs per cycle started, and for ongoing pregnancy.

Results: Average costs of IVF and ICSI hormonal stimulation were € 1630 and € 1585; the costs of oocyte retrieval were 5500 and 725, respectively. The cost of embryo transfer was € 185. Costs per IVF and ICSI cycle started were € 2381 and € 2578, respectively. Costs per ongoing pregnancy were € 10,482 and €10,036, respectively.

Conclusions: Hormonal stimulation covered the main part of the total costs per cycle (on average 68% and 61% for IVF and ICSI, respectively) due to the relatively high costs of medication. The costs of medication increased with increasing age of the women, irrespective of the type of treatment (IVF or ICSI). Fertilization costs (IVF laboratory) constituted 12% and 20% of the total costs of IVF and ICSI. The total cost per ICSI cycle was 8.3% higher than IVF.

Introduction

The introduction of In Vitro Fertilization (IVF) and Intracytoplasmic Sperm Injection (ICSI) has led to a significant increase in couples seeking treatment for infertility. In 1996, one out of 77 newborns in the Netherlands was conceived via IVF or ICSI. By 2000, the frequency had increased to one in every 55 newborns (Kremer *et al.,* 2002). In the Netherlands, both IVF and ICSI are strictly regulated, which has resulted in a total of 13 IVF centers with licensed fertilization laboratories. Fertility teams, consisting of gynecologists, specially trained fertility physicians, fertility nurses, clinical embryologists, laboratory technicians and administrative personnel form the staff of each of these centers. There are also so-called transport clinics where hormonal stimulations and oocyte retrievals are performed, with the actual fertilization (laboratory) and embryo transfer taking place in the affiliated IVF center.

Because IVF and ICSI are expensive procedures, their increased use has been associated with significant economic costs. However, detailed information about the actual costs of IVF and ICSI is scarce. Recently, Collins *et al.,* 2002, presented a literature overview of health economic aspects of IVF and ICSI, focusing on the utilization, cost, and cost-effectiveness of IVF/ICSI. Cost estimates of an IVF treatment cycle for the United States were compared with figures from 25 other countries. The average cost per IVF cycle ranged from $ 1272 to $ 9547 (prices: 2002). Only two studies reported estimates based on actual expenditures of which, one was an older Dutch study (Collins *et al.,* 2002, Goverde *et al.,* 2000).

The costs of ICSI were not included in these studies. Recent cost-estimates differentiating between IVF and ICSI and the different treatment settings for the Netherlands are lacking. Our study provides detailed cost estimates for the different stages of both IVF and ICSI treatment. In addition, these results were used to calculate the costs of IVF and ICSI per treatment cycle and pregnancy in the Netherlands.

Materials and methods

Detailed costs data were collected during a national study that was performed from January 2002 through December 2004. All 13 Dutch IVF centers and transport clinics (n=23) were invited to participate. Within this study, detailed cost data were collected, which made the present costing study possible.

This micro-costing study is based on the 2002 data of resource use and unit prices that were collected at four IVF centers: two academic and two non-academic IVF centers that were assumed to be representative of all Dutch IVF centers; 38% of all the IVF/ICSI cycles that were started in the Netherlands in 2002 were performed in these centers. Additionally, resource use and cost estimates were assessed in one transport clinic.

Within this study we focused on the direct medical costs during treatment. The following cost components were distinguished: costs of the fertility department, costs of medication, costs of the IVF laboratory, and costs of complications due to IVF/ICSI through the first 8 weeks of pregnancy. Based on the availability of eligible sources, either a top-down or a bottom-up approach was used (Table I) (Oostenbrink *et al.,* 2004).

In the top-down approach, cost data obtained from the hospital financial department served as the primary source. These were subsequently allocated to all services of the department on the basis of a predefined formula. For the bottom-up approach, the volume of personnel, equipment and materials for each service was assessed and cost calculations were performed based on purchase prices of materials and equipment and cost standards for personnel. Housing and overhead costs were accounted for by an augmentation of personnel and material costs by 45% (Oostenbrink *et al.,* 2004).

Cost of the fertility departement

The data from the hospital financial departments were insufficiently specific for allocating the information to all the different treatment activities. Expenditures consisted of costs of personnel, diagnostic procedures (including ultrasounds) and materials.

A gynecologist from each center was interviewed for the identification of the resources used during the consecutive treatment stages. In addition, we asked for an estimate of the percentage of patient contacts carried out by a gynecologist and a fertility physician. The time spent on face-to-face contact in each treatment stage was based on the average length of time planned for these consultations.

A 30% charge was added to account for the indirect time spent on matters such as administration, consultation, and preparation (Oostenbrink *et al.,* 2004) Fertility nurses were interviewed to assess material use during follicle aspiration and embryo transfer and the nurse time spent per patient outside the consultation time. The average number of visits per treatment cycle was derived from patients' diaries.

Personnel costs were calculated on the basis of the average functional salary scales. For the costs of the diagnostic procedures the rates assessed by the National Health Tariffs Authority (CTG/ZAio) were used, since these were considered a reasonable reflection of real cost (Oostenbrink *et al.,* 2004). The costs of materials were based on the hospital purchase prices.

Cost of medication

Cost of medication consisted of medication used during the hormonal pituitary down-regulation and ovarian hyper stimulation, including gonadotrophin-releasing hormone (GnRH) agonist, recombinant follicle stimulating hormone (FSH) and human chorionic

Table I Cost components of IVF/ICSI sperm injection

Cost components	Approach	Information source	Units resource use	Cost resource
Cost of fertility department	Bottom-up	Gynecologists	Personnel Diagnostic procedures	Average functional salary scales National Health Tariffs Authority
		IVF-nurses	Direct treatment time Materials	- Hospital purchase prices
		Patient questionnaire	Number of visits	-
Cost of medication	Bottom-up	IVF-registry Standard protocol Standard protocol	Recombinant FSH GnRH-agonists HCG	Pharmacotherapeutic compass (5)
Laboratory costs of IVF/ICSI	Top-down	Manager IVF-laboratory	Personnel	Actual salary scales
		Laboratory technicians	Equipment Materials	Hospital purchase prices Hospital financial records
Costs of complications	Top-down	Hospital admission data	Hospital days	Standard unit prices

gonadotrophin (hCG). The hCG was fixed at 10,000 IU per stimulation, which was the standard procedure in the Netherlands at the time of this study. The actual use of the amount of units of recFSH was taken from the centers' IVF registries. Generally, a long- stimulation protocol was applied. On average, GnRH agonist was used for 25 days per stimulation. For the cost estimates, the costs of 28 days of GnRH agonist were used, which is in line with the actual number delivered per prescription. Cost calculations were based on Dutch wholesale prices (Farmacotherapeutisch Kompas, 2003).

Cost of an IVF laboratory

A top down approach was applied to calculate the costs of an IVF laboratory. Production data of the laboratories were obtained from the annual reports over 2002. A list of personnel was obtained from the managing embryologist of the IVF laboratories. Total personnel costs were calculated using the number of full-time equivalent (FTE) personnel and the reported salary scales.

Equipment was valued based on the centers' actual purchase price inflated to 2002 prices using Dutch price index figures (Oostenbrink et al., 2004). Based on information from two different suppliers of ICSI devices, an equal sum was assumed for each IVF laboratory for the purchase of a complete ICSI device. Costs of equipment per year were calculated according to the annuity method (Oostenbrink et al., 2004). As adequate information on equipment maintenance costs was not available these costs were assumed to be 5% of the equipment purchase prices.

Total materials costs were derived from the financial records of the centers. Expenditures per product were allocated by assessing the used amount of equipment, materials and personnel time per laboratory product with the aid of a questionnaire.

Cost of complications

Costs of complications were limited to the costs of inpatient hospital days, as these were expected to account for the bulk of the costs of complications. Clinical complications related to IVF treatment included ovarian hyper stimulation syndrome and complications resulting from the follicle puncture (Berg and Lundkvist 1992). Data on hospital admissions during 2002 and 2003 were obtained from the annual reports of three academic IVF centers.

Nation-wide figures of the number of cycles that were performed in 2002 were used to calculate the extra cost per treatment cycle due to complications. We used reference prices for the costs of a hospital day in an academic and non-academic center (Oostenbrink *et al.,* 2004) Costs of complications were attributed to their occurrence in general.

The stage of oocyte retrieval

Costs of IVF and ICSI are presented per treatment stage, which were defined as follows: 1) hormonal stimulation, 2) oocyte retrieval, including fertilization (laboratory), 3) embryo

transfer and 4) evaluation, consisting of follow-up visits. The costs of the different stages are presented per type of center (academic, non-academic and transport clinic). Additionally, the weighted average costs are presented on the basis of the number of academic and non-academic IVF centers and the number of transport clinics in the Netherlands.
Now that cryopreservation of residual embryos and cryo embryo transfers has become common practice, cost estimates for these procedures were calculated separately. Total costs of IVF and ICSI treatment for the Netherlands in 2004 were calculated on the basis of figures from the national infertility registration (LIR) (www.lirinfo.nl), and the weighted cost estimates that were inflated to 2004 prices through application of the Dutch general consumer price indices of 2.1% and 1.2% for 2003 and 2004, respectively (http://statline.cbs.nl). These results were used to calculate the 2004 costs per treatment cycle started and per ongoing pregnancy.

Results

Stage 1

The costs of hormonal stimulation consisted of the costs of the fertility department and costs of medication. The mean number of visits to the IVF center during the hormonal stimulation stage was three. Among the fertility departments, the costs varied from € 179 to € 220. The average amount of recFSH per IVF/ICSI cycle was 2370 IU (SD 1095) per stimulation.
Overall, mean total costs of medication (GnRH agonists, rec FSH, hCG) per stimulation cycle were € 1425. The costs of medication showed statistically difference among women in different age groups ($p<0.005$) and increased with increasing age of the women from € 1193 (age 20-24), € 1270 (age 25-29), € 1351 (30-34 year), and € 1547 (age 35-39) to € 1729 (age 40-44).

Stage 2

The costs of oocyte retrieval were composed of department costs, laboratory costs and costs of complications. Department costs included costs of medication during the luteal phase (progesteron daily), and ranged from € 178 to € 237. Costs differences were merely due to differences per center in the number of fertility physicians and gynecologists performing the retrievals. Other differences concerned the planned length of a consultation, which varied from 30 to 45 minutes per oocyte retrieval.
The IVF and ICSI laboratory costs ranged from € 228 to € 347 and from € 436 to € 612 respectively. Laboratory costs of ICSI were higher both because of the relatively high cost of specific equipment and because ICSI fertilization is a more labour-intensive procedure than IVF.
Complication rates related to OHSS were based on information from the annual reports of three academic IVF centers. In the period from 2001 to 2003, a total of 4355 IVF/ICSI cycles

were started in these centers. During this period, 10 patients were hospitalized due to complications of hormonal stimulation, resulting in an incidence of 0.23 per 100 stimulations started. Patients spent on average 9.7 days in the hospital. Based on these figures, the OHSS-related costs were calculated at € 10.40 and € 7.35 per cycle for academic and non-academic centers, respectively.

Data on complications resulting from follicle aspiration were derived from the annual reports of two academic centers. In the period from 2001 to 2003, 11 hospitalizations related to the follicle aspiration were recorded. The incidence was 0.4 per 100 oocyte retrievals. The mean hospital stay was 6.7 days per admission. The costs of complications due to follicle aspiration were € 12.45 and € 8.80 per cycle for academic and non-academic centers, respectively.

Stage 3

The costs of embryo transfer were made up of costs incurred by the fertility department and laboratory costs. Fertility department costs ranged from € 59 to € 79; laboratory costs from € 99 to € 132. The average total cost of an IVF/ICSI embryo transfer was € 185.

Stage 4

During the evaluation, the treatment results are discussed with the couple. The evaluation of patients with a positive pregnancy test after ET varied in length from one to two visits, depending on the procedure followed by the relevant center regarding the point at which patients were referred to their own (local) gynecologist or to a midwife. The mean costs of evaluation of a patient with a positive pregnancy test were € 99.

Resource use for patients with a negative pregnancy test differed: in some centers, the outcome was discussed with the couple during an extra visit, while in other centers, the next contact usually coincided with the start of a new treatment cycle. The mean costs of evaluation for patients with a negative pregnancy test were € 45.

Cryopreservation and cryo-preserved-embryo transfer

Freezing residual embryos is an alternative for repeated stimulation cycles, although the live birth rates resulting from thawed cycles are lower. The annual reports of the IVF laboratories indicated that, on average, 18.9% of all oocyte retrievals resulted in cryopreservation of residual embryos. Costs of cryopreservation after a retrieval resulting in residual embryos were € 141 and € 173 for academic and non-academic IVF laboratories, respectively. Based on these figures, we estimated that the additional cost of cryopreservation per oocyte retrieval was € 29.

Costs of a cryo embryo transfer consisted of laboratory costs (thawing) and department costs (transfer). Total costs ranged from € 302 to € 473 due to different methods followed by the centers. For example, in some clinics cryo-preserved embryo transfers were performed in the

natural cycle. This can be timed by urine luteinizing hormone tests, or by ultrasound, the latter resulting in higher costs. At other centers, cryo embryo transfers take place within an artificially stimulated cycle.

The weighted average costs of a cryo embryo transfer were € 387 (see Table II). Additionally, the evaluation costs after a cryo embryo transfer resulting in a positive pregnancy result were € 111. Cost differences between the evaluation of a cryo cycle and a regular IVF/ICSI cycle were due to the application of prolonged admission of progesteron in artificially regulated cryo cycles.

Cost per treatment cycle and cost per ongoing pregnancy

A total of 15,297 treatment cycles (9178 IVF and 6119 ICSI) were started in 2004. A total of 14,497 embryo transfers were performed, of which 2023 were cryopreserved embryos. An ongoing pregnancy resulted from 21.1% of all IVF cycles that were started and 24% of all ICSI cycles;16.2% of the cryo-preserved transfers resulted in an ongoing pregnancy. Based on these figures, the average cost per ongoing pregnancy was estimated at € 10,290. Costs per treatment cycle started were € 2381 and € 2578 for IVF and ICSI respectively. Costs per ongoing pregnancy resulting from IVF and ICSI were € 10,482 and € 10,036.

Discussion

The 2004 average costs per started IVF and ICSI treatment cycle were € 2381 and € 2578 respectively, and costs per ongoing pregnancy were € 10,482 and € 10,036. Examining the different cost components per treatment cycle, it is evident that the hormonal stimulation stage is the most expensive part of IVF and ICSI, followed by the stage of oocyte retrieval (Figure 1).

Costs of medication constituted more than half of the total costs for both IVF and ICSI (61 and 55% respectively). Approximately 12% of the total costs of an IVF cycle and 20 % of an ICSI cycle were related to the fertilization (laboratory). On the basis of costs per started cycle, ICSI was 8.3% more costly than IVF, which was mainly due to the higher laboratory costs of ICSI. However, costs per ongoing pregnancy of ICSI were lower compared to IVF due to fewer incomplete treatment cycles and higher success rates per cycle.

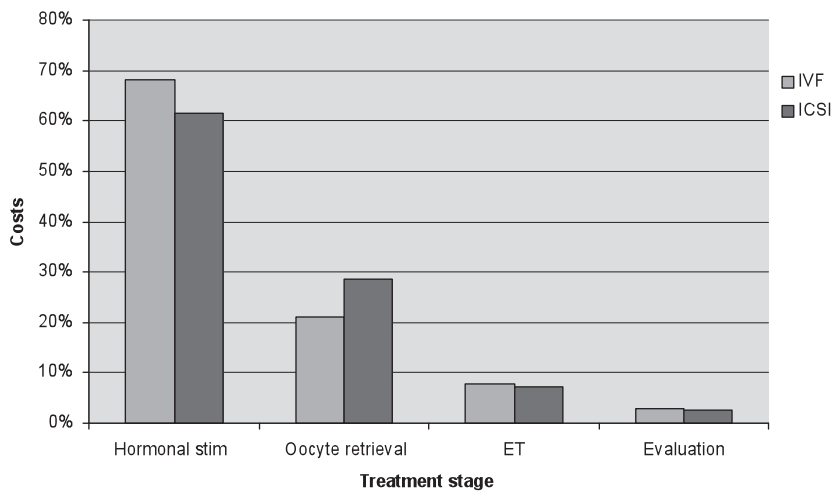
Older women undergoing IVF/ICSI incurred higher costs per cycle than younger women because of the higher mean dosages of recombinant FSH needed during the hormonal stimulation. Additionally, the pregnancy chances decrease with age, resulting in increasing costs per ongoing pregnancy in women aged 34 years and older. Treatment costs varied in

Table II Costs of the different stages of IVF/ICSI (2002 euros)

Hormonal stimulation	Academic center (€)	Non-academic centre (€)	Transport center (€)	Average cost IVF (€)	Average cost ICSI (€)
Department	209 (197-220)	204 (192-215)	179	189	189
Medication				1443 (301-3785)	1394 (301-3714)
Total				1632	1583
Oocyte retrieval[a]					
Department	208 (178-237)	217 (206-228)	225	220	220
Laboratory IVF	250 (228-272)	321 (294-347)	N.A.	277	-
Laboratory ICSI	474 (436-512)	548 (484-612)	N.A.	-	503
Total				498	723
Embryo transfer					
Department	76 (76-75)	67 (59-75)	79	76	76
Laboratory	105 (89-120)	115 (99-132)	N.A.	109	109
Total				185	185
Evaluation costs					
Pregnancy pos.	51 (50-53)	104 (92-116)	114	99	99
Pregnancy neg.	23 (0-46)	28 (0-57)	57	45	45
Cryo-embryo transfer					
Department	108 (106-111)	154 (92-216)	140	135	135
Laboratory	231 (197-265)	286 (257-315)		252	252
Total				387	387

Note: Cost ranges between brackets representing minimum and maximum cost estimates since the study was performed in two centres per hospital type. N.A.:=not applicable.
[a]Costs of cryo-preservation not included.

Figure 1 Price portions of the treatment stages of IVF/ICSI



the different settings. Generally, costs in academic centers were lower compared to non-academic centers.

The costs of an embryo transfer after cryopreservation were higher than the costs of a fresh embryo transfer (€ 387 versus € 185) due to higher laboratory costs. Extra costs were related to the thawing of cryo-preserved embryos (personnel time and materials) and the administrative procedures for preservation of residual embryos.

To our knowledge, this is the first study in which the opportunity costs (i.e. actual costs) of IVF and ICSI are presented in detail on the basis of data from a representative number of IVF centers. Our findings were in line with the cost estimates reported earlier by Goverde *et al.,* 2000. The costs of medication reported in that study were relatively low, probably due to the standard use of human menopausal gonadotrophin, which is less expensive than the current IVF stimulation protocol that uses recombinant FSH. The costs of ICSI were not reported in their study.

In the international literature, the cost estimates of IVF vary widely (Collins *et al.,* 2002. However, most estimates are based on charges, which limit the comparability with the findings from our study. For reasons of comparison, we conducted a supplementary literature search for cost data following the period searched by Collins. English language publications

were identified through MEDLINE using the keywords IVF, ICSI, cost(s) and cost-effectiveness over the period 2001 to May 2006, which resulted in 14 publications that described the costs of treatment with IVF and/or ICSI (Table III).

Four studies originated from northern European countries (Sweden, Norway and Finland), two from the United Kingdom, one from Belgium, one from Hungary, four from the Netherlands and three from the United States. Original estimates in pounds sterling and US dollars were converted to Euros. Additionally, all prices were inflated to 2004 costs using Dutch consumer price index rates. The highest cost estimates were those of Kansel-Kalra *et al.,* 2005, although how these estimates were calculated remained unclear, as detailed information was lacking. The lowest estimates were presented by Kovacs *et al.,* 2004.
Only two studies (Lloyd *et al.,* 2003; Fiddelers *et al.,* 2006), presented cost estimates that were based on actual expenditure. The study of Fiddelers was performed in the Netherlands. The estimates were derived from one, relatively small Dutch IVF center and no distinction was made between the costs of IVF and ICSI. Most cost estimates in this study were relatively high compared to the 'harmonized Dutch cost estimates' calculated for an integrative study in the Netherlands on the basis of information from six IVF-related studies financed by the Dutch Organisation for Health Research and Development (ZonMW). It was assumed that the variation in costs was due to differences in the size of this IVF center and the adopted method of cost calculation.
In four studies, the costs of IVF and ICSI were reported separately (Kjelberg *et al.,* 2006; Kovacs *et al.,* 2004; Silverberg *et al.,* 2002; Strandell *et al.,* 2005). Costs of an ICSI cycle averaged 11% more than the costs of IVF, with the exception of the estimates presented by Kovacs et al, who reported ICSI costs that were more than 30% higher than IVF costs (Kovacs *et al.,* 2004). In general, the intercountry comparability of the cost of IVF and ICSI was low, due to differences in the definition of a treatment cycle, differences in study questions and differences in health-care setting.
According to the figures in the ESHRE report of 2006, the IVF centers in most European countries are relatively small compared to the Dutch centers (ESHRE, EIM, 2006). Overall, 14% of the European centers in the ESHRE registry performed more than 1000 cycles in 2002 and almost 16% of the centers performed fewer than 100 cycles. Of the 13 Dutch IVF centers, eight reported performing at least 1000 treatment cycles (range 1171-2027) in 2004, and in 4 centers the number of cycles performed ranged from 610 to 952. Differences in the international cost estimates may partly result from differences in the size of the centers.

Generally, the financial departments of hospitals are not tailored to register resource use on the level of patient groups, which inhibited a uniform methodology for calculating costs. The bottom-up approach that was used for most cost components results in a more precise

allocation of costs to a service although the actual expenditures may have been underestimated, as this method does not consider 'wasting' costs. Furthermore, our estimates were based on patients who actually started with hormonal stimulation. A small number of patients may have quit treatment during the stimulation phase before the start of medication. In this study, we focused on the direct medical costs. We assumed that indirect costs, such as costs of productivity losses were relatively small.

Diagnostic work-up costs were not included in this study. Although, strictly speaking, these costs are not within the province of IVF/ICSI treatment, these costs must be taken into consideration in the broader context of the IVF/ICSI program. During the diagnostic work-up, couples are extensively counseled about the treatment. In couples with severe male infertility diagnostic tests are performed to inform the couples about the possibility of transferring genetic abnormalities into offspring. We calculated the average costs of the diagnostic work-up preceding IVF at € 286 (data not shown). The extra costs of genetic diagnostics preceding ICSI varied considerably, and ranged from €31 to € 1836. Given these findings, further research is needed to study the cost-effectiveness of these diagnostic procedures.

Acknowledgements

The authors would like to thank all gynecologists, fertility physicians and nurses, embryologists and laboratory technicians and all others persons, who provided data on which our study is based. We thank A. Wetzels (IVF-laboratory, University Medical Centre Nijmegen) for his support in calculating laboratory costs.

Table III Overview of IVF/ICSI cost estimates from international studies

Study	Country	Focus of the study	Original currency	Original price (year)
Eijkemans et al., 2005	Netherlands	Patient-tailored treatment algorithm for anovulatory infertility.	Euro	2002
Lukassen et al., 2005	Netherlands	SET vs DET	Euro	2003
Fiddelers et al., 2006	Netherlands	SET vs DET	Euro	2003
Gerris et al.,2004	Belgium		Euro	2003
Granberg et al., 2003	Sweden	Laparascopic surgery vs IVF in patients with tubal factor infertility	U.S. dollar	2001
Kjellberg et al., 2005	Sweden	SET vs DET	Euro	2004
Strandell et al., 2005	Sweden/ Danmark	Immediate IVF vs salpingectopmy before IVF.	Euro	2004
Koivurora et al., 2004	Finland	Prenatal and neonatal costs after IVF vs spontaneous conception	Euro	2003

	Bases of estimates	Costs per cycle 2004 (€) IVF + medication ICSI + medication Cryo ET	Main conclusions of the study
	Hospital costs + medication: inflated figures from the study of Goverde et al	IVF 1,883 - -	A treatment strategy of CC+FSH+IVF was efficient for women aged < 30 years with normal androgen levels. For women > 30 years with elevated androgen levels, FSH may be skipped
	Hospital costs + medication: reimbursement	IVF 2585 - -	Two cycles with SET were equally effective as one cycle with DET, and the medical costs were the same
	Hospital costs; unit costs from the financial department. Including medication costs. Laboratory costs based on cost price calculation.	IVF/ICSI 3491	The extra costs of DET per additional pregnancy compared with elective SET were € 19,096. These costs were due to the higher costs of pregnancy after DET
	Average reimbursement of IVF/ ICSI, including cost of medication	IVF/ICSI 2477 -	
	Hospital: standardized hospital charges (partly based on DRG's); Medication: mean costs of standardized stimulation protocol	IVF 3378 - Cryo ET 1057	Only small differences were found between the average costs per delivery after tubal surgery and treatment with three IVF cycles
	Hospital costs: DRG Medication: sales prices Costs of complication not included	IVF 4174 ICSI 4627 Cryo ET 994	SET was superior to DET (lower average total costs)
	Hospital costs: Standardized Hospital charges (partly based on DRG); Medication: sales prices	IVF 4275 ICSI 4748 Cryo ET 1038	The incremental cost-effectiveness ratio of salpingectomy prior to IVF was € 9306 compared to immediate IVF
	Hospital: hospital data (not specified). Medication: social insurance institution Finland	IVF 3247 - -	Total health care costs for singleton and IVF twins were € 5780 and € 5580 respectively

Table III (continued)

Study	Country	Focus of the study	Original currency	Original price (year)
Sykes et al., 2001 (20)	U.K.	Modelled evaluation of three alternative hormonal stimulations: rec FSH, urinary FSH and HMG	U.K. pound	1999
Lloyd et al, 2003	U.K.	Evaluation of ovarian stimulation with highly purified hMG versus rec FSH	U.K. pound	
Kovacs et al., 2004	Hungary	Hormonal stimulation using CC + hMG vs GnRH + hMG	U.S. dollar	Not stated
Silverberg et al., 2002	U.S.	Modelled evaluation of rec FSH vs urinary FSH	U.S. dollar	Not stated
Kansal-Kalra et al., 2005	U.S.	Modeled evaluation of a strategy of immediate IVF vs gonadotropin therapy for unexplained infertility	U.S .dollar	2003
Hatoum et al, 2005	U.S.	Modeled evaluation of urinary FSH vs recFSH	U.S. dollar	2003

Note: CC, clomiphene citrate; cryo-ET, cryo-preserved-embryo transfer, DET, double embryo transfer; DRG, diagnosis related group; FSH, follicle-stimulating hormone; GnRH-a, gonadotropin-releasing agonist; hMG, human menopausal gonadotropin; OHSS, ovarian hyperstimulation syndrome; recFSH, recombinant FSH; SET, single embryo transfer.

[a] Proxies were used if the price year was not reported: UK £ = € 1.43882, U.S. $ = € 0.825785

	Bases of estimates	Costs per cycle 2004 (€) IVF + medication ICSI + medication Cryo ET	Main conclusions of the study
	Hospital: average prices from 20 IVF; average dose of medication per IVF attempt: based on expert panel; hospital costs and duration due to OHSS: expert panel	IVF 2456-3001 - Cryo ET 539	RecFSH was a cost-effective stimulation strategy
	Hospital treatment: Hospital financial department; Medication: sales prices	IVF/ICSI 3754-4253	Highly purified hMG and rec FHS were equally effective, but hMG was less expensive per cycle
	Hospital costs: not stated Medication: patient charts	IVF 1206-1300[a] ICSI 1637-1731[a]	Costs per cycle were higher with GnRHa+ gonadotropin, however, the cumulative costs were reduced by the time a clinical pregnancy was achieved
	Hospital costs + medication: 70% of billed charges (=reimbursement level of managed care)	IVF 10,164-10,486[a] ICSI 11,417-12,810[a] Cryo-ET 1566[a]	Rec FSH was more cost-effective (more effective at lower costs) than urinary FSH
	Hospital costs + medication: inflated figures from the study of Goverde et al	IVF 12,646 - -	Considering the risk of high order multiple pregnancy, immediate IVF was more costly than gonadotropins prior to IVF.
	Hospital costs: figures from the study of Silverberg et al Medication: wholesale acquisition costs	IVF 10,263 - -	Costs of IVF treatment with urinary FSH were lower in comparison to treatment with recFSH.

Chapter | 11

Cost-effectiveness of IVF/ICSI for sub groups of subfertile patients: a Prospective Cohort - Waiting List Study

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Abstract

Background: A few countries have guidelines for In Vitro Fertilisation (IVF), using the diagnostic category, age of the woman and duration of subfertility. The cost-effectiveness of these guidelines is unknown, and the evidence-base exists only for bilateral tubal occlusion, not for the other diagnostic categories. We aimed to establish the cost-effectiveness of starting IVF compared to waiting for one more year, depending on prognostic patient characteristics.

Methods: A prospective cohort study included 5962 couples eligible for IVF or ICSI treatment according to the Dutch IVF/ICSI guideline, registered in a national waiting list in The Netherlands. Chances of treatment-independent ongoing pregnancy were estimated from the waiting list observations and chances with IVF from follow-up data of couples that did start treatment. Prognostic factors considered were female age, duration of subfertility, primary or secondary subfertility and diagnostic category. Costs of IVF were determined on a representative sample of patients. A cost-effectiveness comparison was made between two scenario's: I) wait one more year and then undergo IVF for one year and II) direct IVF during one year, with treatment-independent pregnancy chances after that year. Comparisons were made for strata determined by the predictive factors and the outcome was live birth.

Results: The gain in pregnancy chances of the direct IVF scenario versus postponed IVF increased with age, but was independent from diagnostic category or duration of subfertility. Contrary, the corresponding increase in costs primarily depended on diagnostic category and duration of subfertility. The cost-effectiveness ratio for endometriosis was just below € 10,000 per live birth from age 34 onwards at 2 years duration. For unexplained subfertility at three years duration, the ratio was below € 30,000 per live birth from age 32 onwards. It reached € 20,000 per live birth only with 4 years duration at age 34 and older. The cost-effectiveness ratio was in between for the other diagnostic categories.

Conclusions: Postponing IVF saves money against a small loss in overall live birth rate. The duration at which starting IVF becomes cost-effective depends on diagnostic category, female age and society's willingness to pay for an extra live birth.

Introduction

A few countries have guidelines for In Vitro Fertilisation (IVF) (Dutch Society for Obstetrics and Gynaecology, guideline no. 09, 1998; NICE. Clinical guideline 11, 2004). The guidelines recommend, for given combinations of diagnostic category and age of the woman, at which duration of subfertility IVF should be started. The cost-effectiveness of these guidelines has never been assessed.

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 subfertility. Yet, it is only for the tubal indication group that evidence from a randomised controlled trial is available (Soliman *et al.,* 1993). The evidence base for other categories is considered to be weak or lacking (Hughes *et al.,* 2004; Pandian *et al.,* 2005).

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 spontaneous conception or start IVF. For idiopathic, mild male or cervical subfertility, Intra Uterine Insemination (IUI) is the only treatment option prior to IVF. The usefulness of IUI is however being debated (Pashayan *et al.,* 2006) and further, it is not self-evident that a couple should start IVF directly after failed IUI; a waiting time could be indicated to profit from a remaining spontaneous pregnancy chance before IVF treatment is commenced, given the high cost and burden of IVF. Therefore, an evidence-based comparison of expectant management versus IVF is needed for all diagnostic categories. Within current practice, a randomised comparison would not be feasible. Instead, the waiting period before the actual start of IVF could be used to estimate the treatment–independent pregnancy chances of couples that are going to start IVF.

Though it is well recognised that pregnancy chances with IVF depend on age of the woman and on duration of subfertility, IVF appears to be equally effective for the various diagnostic categories for subfertility (Templeton *et al.,* 1996; Lintsen *et al.,* 2007). Similarly, age and duration are predictive of treatment-independent pregnancy chances, but in this case diagnostic categories differ substantially. Because the same factors are predictive for both treatment-independent and treatment-related pregnancy, we might infer that the relative efficacy of IVF over waiting longer would depend only slightly or not at all on patient characteristics. In a modelling exercise, Mol *et al.,* 2000, showed that the cost-effectiveness strongly depends on the age of the female partner. However, this remains to be assessed on prospective data and for other predictive factors.

The aim of the current study is to determine the cost-effectiveness of IVF compared with waiting for a longer period, according to prognostic factors female age, duration of subfertility, type of subfertility (primary or secondary) and diagnostic category.

Materials and Methods

Subjects

Between 1-1-2002 and 31-12-2003, a national cohort study was executed in the Netherlands that prospectively registered all patients in IVF clinics on a waiting list, at the moment of indication for IVF or ICSI by their gynaecologist. During 2004, the registered data were cross-checked with the IVF treatment registries of the clinics, to see whether the patients had actually started IVF or not. Patients that 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. From the data collected, prediction models were developed for the chance of treatment-independent pregnancy, as observed during the period on the waiting list (Eijkemans *et al.,* 2008) and for the chance to become pregnant with IVF/ICSI (Lintsen *et al.,* 2007). The costs of IVF/ICSI were determined on a representative sample of patients undergoing treatment in 5 participating clinics (Bouwmans *et al.,* 2008a). The current study integrates these findings.

Cost-effectiveness analysis

The aim of the study was to assess the cost-effectiveness of IVF/ICSI compared to waiting longer, for subgroups of patients. The methodology followed is similar to the one used in a previous study in anovulatory patients (Eijkemans *et al.,* 2005): comparisons between treatment scenarios were made for subgroups of patients defined by the prognostic factors female age, duration of subfertility, type of subfertility and diagnostic category. Two treatment scenarios were compared: I) wait one year, then one year of IVF and II) direct IVF during one year, then one year no treatment. The time horizon of the analysis was therefore two years, and is the same for both scenarios. We do not have direct observations of outcomes for both scenarios, because no randomized data are available. However, the relevant chances of the periods with and without treatment in both scenarios may be obtained from our predictions models on IVF chances (Lintsen *et al.,* 2007) and on chances on the waiting list (Eijkemans *et al.,* 2008).

The effectiveness measure of the study was a live birth following ongoing pregnancy. Ongoing pregnancy was defined as foetal heart beat activity on ultrasound after at least 8 weeks gestation. Our data contained ongoing pregnancy and not live birth. Therefore

ongoing pregnancy was converted to live birth using published data of Arce *et al.,* 2005: 92% (95% confidence interval: 88-96%) of ongoing pregnancies will result in a live birth.

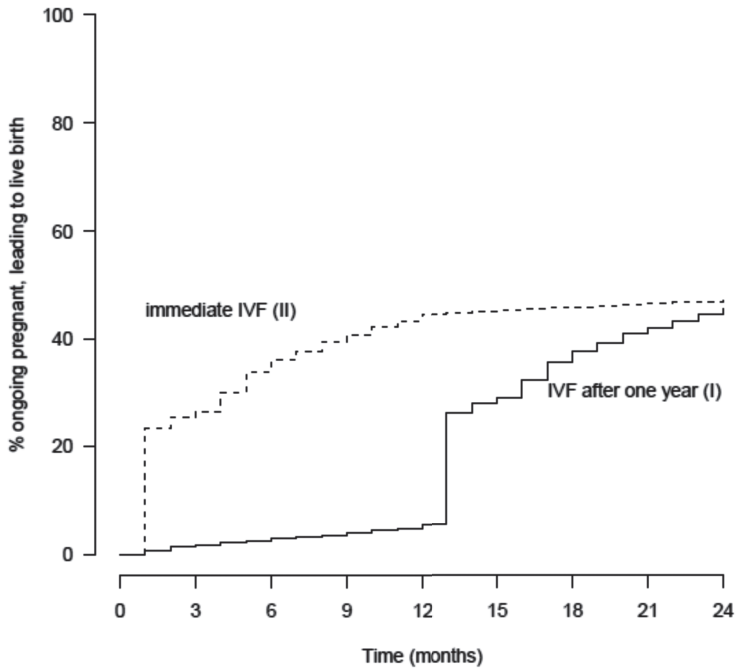
The prediction models for treatment-independent pregnancy ('treatment-independent' model) (Eijkemans *et al.,* 2008) and for pregnancy following IVF (IVF model) (Lintsen *et al.,* 2007) were converted to live birth and subsequently used to compare the live birth chances of the two treatment strategies for various patient profiles:

Scenario	Model calculations
I: Postpone IVF for 1 year	'treatment independent' chances within 12 months leading to live-birth **PLUS** IVF pregnancy chances within 12 months leading to live-birth, with 1 year added to the age and duration of subfertility of the patient and weighted by the chance of not being pregnant after waiting for 1 year.
II: Direct IVF for 1 year	IVF pregnancy chances within 12 months leading to live-birth **PLUS** 'treatment independent' pregnancy chances within 12 months leading to live birth, with 1 year added to the age and duration of infertility of the patient and weighted by the chance of not being pregnant within 1 year after the start of IVF

Figure 1 shows the principle. Scenario I starts with one year of rather low treatment-independent chances, and stays far behind scenario II (direct IVF). However, in the second year, scenario I almost catches up with II.

Comparisons were made for patient strata determined by the factors in the prediction models. To illustrate the calculations in detail, reference case analyses were performed using four "example" patient profiles: unexplained subfertility and endometriosis both at female ages 30 or 38 years and all with primary subfertility of 3 years duration.
The health economic perspective was that of society. We therefore included direct and indirect medical and non-medical costs. The costs of the treatment-independent pregnancy attempts were assumed to be zero. The direct medical costs of IVF/ICSI were determined from the per-cycle cost estimates from Bouwmans *et al.,* 2008a. To this we added an estimate of 596 euro per cycle as direct non-medical costs due to absence from work (Bouwmans *et al.,* 2008b). The resulting total cost per cycle were applied to the data from all patients starting

Figure 1 Cumulative chances of ongoing pregnancy leading to live birth, against time with the two scenarios for IVF



IVF/ICSI treatment used in Lintsen *et al.,* 2007 and for each patient, the costs over a 1-year period of treatment were aggregated. On these data, a prediction model for the costs of IVF over a 1-year period was developed using the same four factors as used in the prediction models for pregnancy chances, using linear regression analysis. The resulting model equations are available from the authors on request.

In case of an ongoing pregnancy leading to live birth, the costs of subsequent delivery and neonatal care were added to the costs of treatment. We used the estimates from (Lukassen *et al.,* 2004) for IVF conceived pregnancies: € 2549 for a singleton and € 13,469 for a twin pregnancy. In a sensitivity analysis, we used recent cost estimates for delivery and neonatal care following IVF and naturally conceived pregnancies from Chambers *et al.,* 2007. The age-standardised estimates for singletons were € 4624 and € 4098 (difference: € 526) with IVF and naturally conceptions respectively. For twin pregnancies, the estimates were € 14,114 and € 13,350 (difference: € 764) respectively. The cost differences between IVF and

treatment-independent pregnancies found by Chambers *et al.,* 2007 were also applied in the standard analysis with costs of IVF pregnancies from Lukassen *et al.,* 2004. We further assumed that 21.5% of IVF pregnancies were twins, as registered for the Netherlands in 2003 (Kremer, National IVF figures, 2007), and 1% of treatment-independent pregnancies.

The cost-effectiveness comparison was made between scenarios (II) (direct IVF) and (I) (first wait for 1 year). The difference in live birth rate (effectiveness) between the scenarios was calculated as well as the difference in costs. The cost-effectiveness ratio, the cost difference divided by the effectiveness difference, indicates the extra costs per extra live birth of (II) versus (I). In order to translate the cost-effectiveness ratio to a policy recommendation, for each age the duration of subfertility was determined at which a pre specified threshold for the cost-effectiveness ratios is attained. Following standard methodology in economic appraisals, costs and effects were discounted to present values. A discount rate of 3.5% was used for both costs and effects, as recommended by NICE, 2008.

The statistical uncertainty in the results was assessed by a bootstrapping method with 5000 replications. We used samples from the original waiting list cohort data, including the subsequent IVF treatment data, and re-estimated the prediction models for treatment-independent pregnancy chances and for pregnancy chances and costs of IVF on each sample. The resulting model-predictions for the four base-case patient profiles were used to assess the difference in costs and effects of the two scenarios. From these resampled differences in costs and effects, a cost-effectiveness acceptability curve was derived that shows, for the four patient profiles, the proportion of samples in which direct IVF is cost-effective, given a threshold value for the cost-effectiveness ratio.

Results

Characteristics of the study inclusion have been published before (Lintsen *et al.,* 2007; Eijkemans *et al.,* 2008). Briefly, there were 6221 patients rightfully included on the waiting list. Of 5962 patients, the follow-up could be established, and they formed the basis of analysis. The estimated proportion of treatment-independent ongoing pregnancies after 12 months was 9% (Eijkemans *et al.,* 2008). Further, 4928 couples started IVF, resulting in an ongoing pregnancy rate of 45% within 12 months (Lintsen *et al.,* 2007).

Table I shows, for the four reference case patient profiles, the treatment-independent live birth rates in the first and second year, the IVF live birth rates in the first and second year and the comparison between the two scenarios. The treatment-independent pregnancy chances

Table I Chances of pregnancy leading to live birth of the two strategies, for four selected patient profiles

	patient profiles with primary subfertility of 3 years and:			
Diagnostic category Age	**Unexplained 30**	**Unexplained 38**	**Endometriosis 30**	**Endometriosis 38**
Treatment-independent chance in year 1	0.127	0.089	0.037	0.026
Treatment-independent chance in year 2	0.111	0.079	0.032	0.023
IVF chance in year 1	0.495	0.323	0.423	0.268
IVF chance in year 2	0.484	0.273	0.413	0.226
Chance with Scenario I, postponing IVF for 1 year*	0.550	0.338	0.435	0.246
Chance with Scenario II, direct IVF*	0.551	0.376	0.442	0.285
Chance difference II – I (Delta P)	0.001	0.038	0.007	0.039

* Pregnancy chances leading to live birth per scenario are calculated from the relevant year-specific chances applied to those couples that didn't become pregnant in the previous year. E.g. Pregnancy chance with Scenario II, direct IVF = 0.495 + (1-0.495)*0.111 = 0.551.

differ between diagnostic categories and are lower for older age. IVF chances also decline with age, but they show less dependence on diagnostic category. All chances are lower in the second year than in the first year, but the differences vary over patient profiles. The chances with the direct IVF scenario (II) are slightly higher than with the postpone IVF scenario (I) and the difference depends more strongly on age than on the diagnostic category. The difference varies from 0.001 for unexplained subfertility at 30 years to 0.039 for endometriosis at 38 years.

Table II shows the costs and the cost effectiveness comparison for the four reference case patient profiles. With older age, IVF becomes more costly, because more treatment cycles are needed to compensate for the decreased chances per cycle, and because the cost of medication per cycle increases (Bouwmans *et al.,* 2008a). For each patient profile, the costs of IVF as well as the costs of delivery and neonatal period are higher in scenario II, direct IVF, than in scenario I, postponing IVF. Therefore, in total, direct IVF is more costly than postponing IVF. The undiscounted cost-effectiveness ratio, obtained by dividing the cost difference by the live birth rate difference, is very high for unexplained subfertility at age 30: one extra live birth gained by direct IVF as compared to postponing IVF costs 574,000 euro. The ratio is lowest for endometriosis at age 38: 6300 euro per live birth. Discounting has a profound impact, making the very high ratio considerably lower. Using the costs for delivery and neonatal care from Chambers *et al.,* 2007 had little impact on the cost-effectiveness ratios.
The statistical uncertainty of the estimated differences in costs and effects, derived from 5000 bootstrap samples from the original cohort data, was assessed for the four patient profiles. The corresponding uncertainty in cost-effectiveness ratios is represented as cost-effectiveness acceptability curves in Figure 2. At age 38 we may be more than 95% certain that direct IVF is cost-effective at a 15,000 euro threshold level for endometriosis and at a 27,000 euro per live birth level for unexplained infertility.

Comparisons for all possible combinations of couple characteristics, restricted to female ages above 30 and primary subfertility, are depicted in Figures 3a and 3b. Figure 3a shows the differences in live birth rates. The difference becomes larger with age, reaching a maximum at age 38. The difference at a given age is almost the same for the various diagnostic categories or durations of infertility. The difference in costs between the two scenarios (not shown), did hardly depend on age, but strongly on diagnostic category and on the duration of infertility. The cost difference was lowest for endometriosis, around 400 euros, decreasing with duration of infertility by 25 euros per year. The highest cost difference was seen for unexplained subfertility, with values around 800 euros, decreasing with duration of infertility by 75 euros per year.

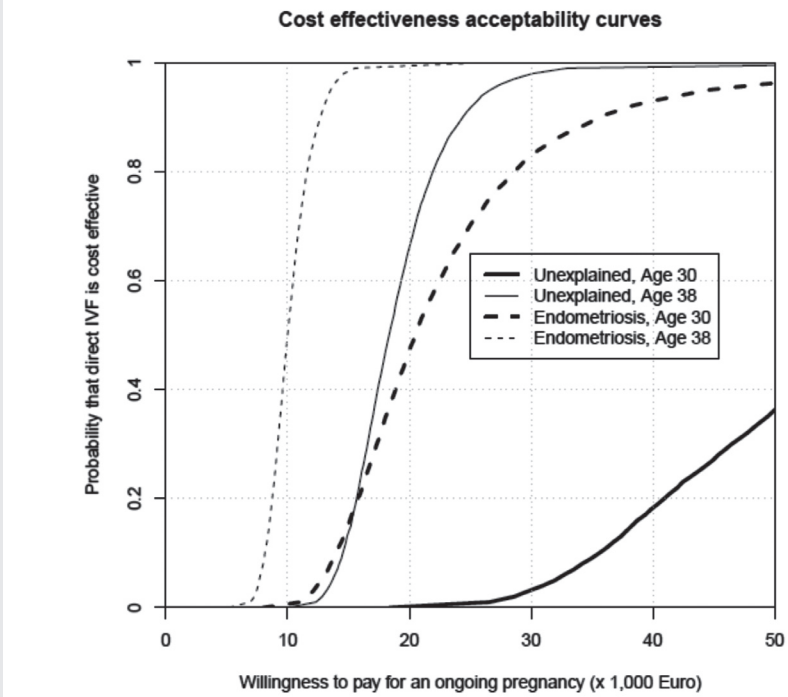
Table II Costs of IVF treatment and costs of delivery and neonatal period of the two strategies, for four selected patient profiles (Euros)

	patient profiles with primary subfertility of 3 years and:			
Diagnostic category	**Unexplained**	**Unexplained**	**Endometriosis**	**Endometriosis**
Age	**30**	**38**	**30**	**38**
Costs of IVF treatment in year 1	3,421	4,295	3,622	4,496
Costs of IVF treatment in year 2	3,443	4,385	3,644	4,586
Costs of Scenario I, postponing IVF for 1 year				
IVF treatment	3,005	3,993	3,508	4,468
Delivery and neonatal period	2,341	1,410	2,027	1,131
Total	5,346	5,402	5,535	5,599
Costs of Scenario II, direct IVF				
IVF treatment	3,421	4,295	3,622	4,496
Delivery and neonatal period	2,543	1,694	2,111	1,348
Total	5,964	5,989	5,733	5,844
Total cost difference II – I (Delta C)	618	586	198	245
Cost effectiveness ratio				
(DeltaC / DeltaP*)	574,000	15,500	30,200	6,300
discounting with 3.5% per year	58,300	17,100	19,700	9,400
discounting, alternative costs**	58,500	18,600	21,100	11,100

* DeltaP = Chance difference between scenarios II and I, from Table I

** Costs for delivery and neonatal care from Chambers *et al.*, 2007

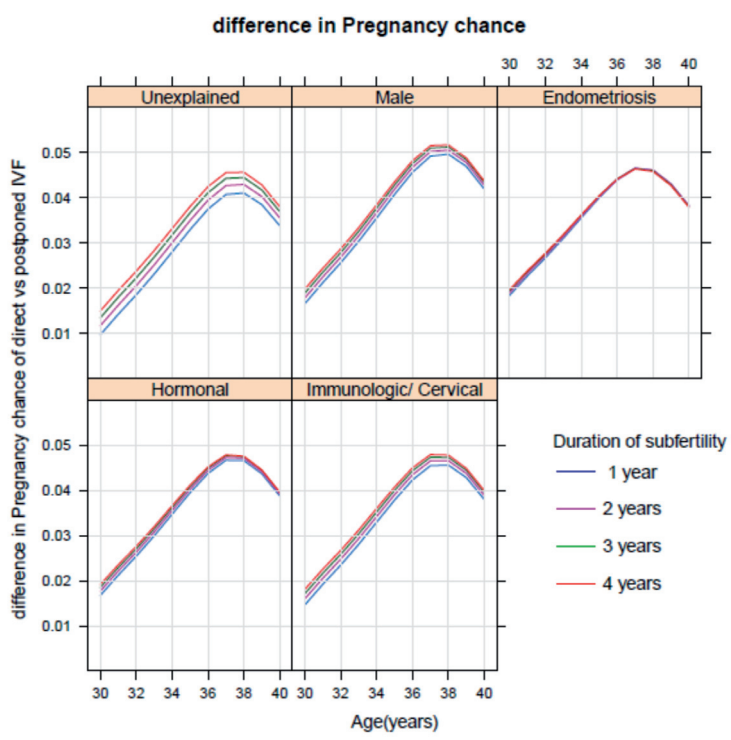
Figure 2 Results of a bootstrapping procedure with 5000 replications from the original cohort data (n= 5962): Cost-effectiveness acceptability curves, representing the chance that direct IVF is cost-effective against Society's willingness to pay for a live birth



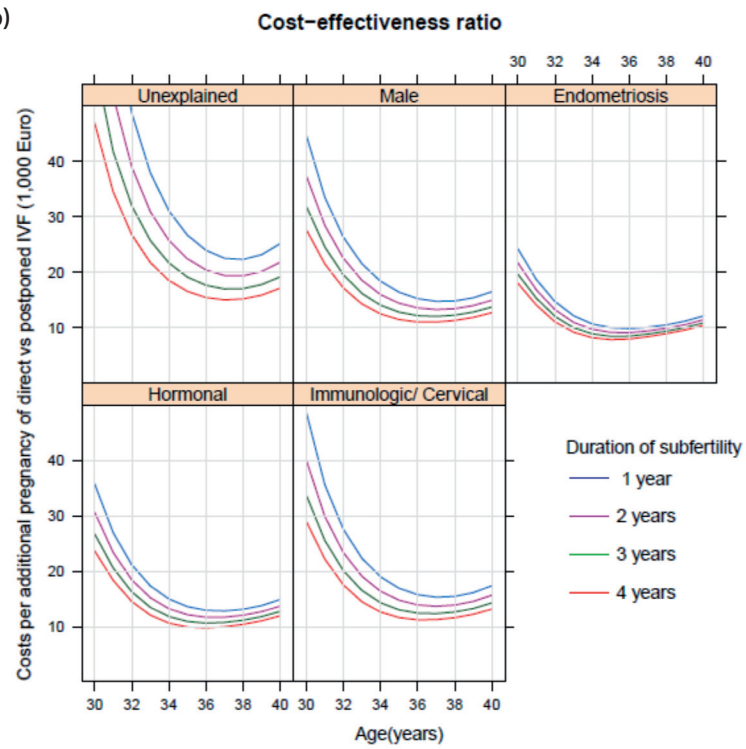
In Figure 3b, the cost-effectiveness ratio is depicted. The cost-effectiveness of direct IVF is mainly dependent on diagnostic category and age and less on the duration of infertility. A steep decline with age is visible, followed by a slight increase from age 36 onwards. This pattern is clearly related to the patterns in effect-differences and cost-differences from Figures 3a and 3b respectively. For unexplained subfertility at three years duration, the ratio is below € 30,000 per live birth from age 32 onwards. It reaches € 20,000 per live birth only with 4 years duration at age 34 and older. At a € 10,000 per live birth level, direct IVF is cost-effective only for endometriosis from age 33 onwards, at 3 years duration. For the other indications, the cost-effectiveness ratio stays above € 10,000 per live birth, for all durations and ages. For male subfertility, we cannot conclude cost-effectiveness from our results, as there was no differentiation on the waiting list between mild and severe male infertility.

Figure 3 Difference in live birth chances (3a) and the corresponding cost-effectiveness ratio (3b) between 'Direct IVF' and 'postponing IVF for one year', in relation to female age. Separate panels for diagnostic categories and separate curves for duration of infertility

(a)



(b)



Discussion

We conducted a cost-effectiveness analysis of starting IVF in subfertile couples versus postponing IVF for one year, stratifying on diagnostic category, age, duration and type of subfertility. Observations from a large prospective study on IVF pregnancy chances and costs in the Netherlands, including estimates of treatment-independent pregnancy chances while on the waiting list for IVF, formed the empirical basis of the study. Results showed that the cost-effectiveness of IVF is most plausible for endometriosis, irrespective of the duration of subfertility or age. For unexplained subfertility, IVF may be postponed for women under 32

until the duration of subfertility reaches more than 3 years, mainly because treatment-independent chances are still considerable while IVF chances after one year will hardly have decreased.

The eventual loss in chance of a live birth due to postponing IVF for one year is less than 6% for all cases and mainly depends on age (Figure 3a and Table I). The couples that would otherwise have a live birth with IVF in the first year, will either have a live birth after treatment-independent pregnancy during that first year, or from a pregnancy with IVF in the following year. The main effect of direct IVF compared to postponing IVF is therefore that treatment-independent pregnancies are replaced by IVF pregnancies, against considerable extra costs. In a recent simulation study, Habbema *et al.,* 2009 showed a similar finding.

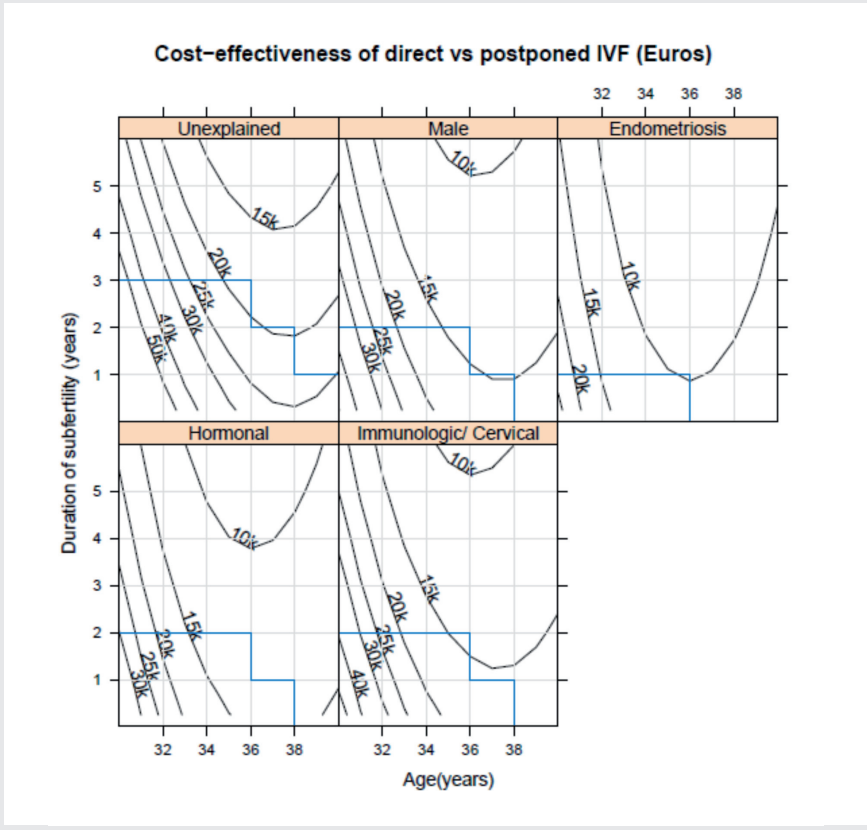
From the present results, we can evaluate the current guideline for IVF in the Netherlands (Dutch Society for Obstetrics and Gynaecology, guideline no. 09, 1998). According to this guideline, the time when to start IVF or ICSI treatment depends on the cause and duration of subfertility, the seriousness of the disorder and women's age. When the problems are caused by pathology of the tubal function, such as tubal blockage (1) or severe endometriosis (2), IVF should be offered directly. In case of relative tubal pathology, the infertility should be at least of 1 or 2 years duration. If there is no reason found (3), IVF is only indicated after a period of infertility of at least three years and should be preceded by intra uterine insemination (IUI) treatments while waiting for the required duration of subfertility. Minimal endometriosis is treated as unexplained subfertility (3). In case of ovulation disorders (mainly caused by polycystic ovary syndrome (PCOS) (4), at least twelve 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), and for mild male subfertility (6), if the multiplication of the volume, concentration and motility (VCM) of the semen analyses is between 1-10 million, IVF is offered after a duration of at least two years and is preceded by IUI. For severe male subfertility, (VCM < 1 million), there is a direct indication for ICSI. For all diagnostic categories applies: IVF can be offered 1 or 2 years earlier, if women are over 36 years or 38 years, respectively. There is no absolute age limit, but the guideline advises not to treat women over 40 years of age, because of poor treatment outcome. In Figure 4, showing an alternative representation of the relationship of the cost-effectiveness of direct IVF with diagnostic category, duration of infertility and age, we also depicted the durations at which IVF would be indicated according to the Dutch guideline. For ages over 34 years, the duration according to the guideline coincides with levels of the cost-effectiveness ratio approximately between 15,000 and 25,000 euro per live birth. For ages below 34, the durations according to the guideline correspond with higher levels of the cost-effectiveness ratio, reaching 56,000 euros per live birth for unexplained subfertility at age 30.

The costs per extra ongoing pregnancy were above 10,000 euros for most combinations of diagnostic category, age and duration. Depending on the threshold level of the CE ratio per live birth, direct IVF becomes cost-effective, but this depends on the female age: the cost-effectiveness ratio decreases with age, reaching a minimum around age 35-37, after which it increases again. There is no consensus on the level of costs per extra live birth that is acceptable. This is in contrast with the standard in health economics, with the Quality Adjusted Life Years (QALY) as effectiveness measure. There, a threshold between 30,000 and 80,000 euro per QALY is generally considered as the limit of acceptability (NICE, 2008). Up till now, no studies have been published that translated a pregnancy leading to birth of a child into a gain in QALY for the parents.

Limitations of our study are the following:
We applied estimates of chances with IVF, excluding frozen embryos, for which we had no data. However, it is plausible that the same factors influencing IVF pregnancy chances will affect the chances with frozen embryos. Further, our cost calculations include a 'punishment' in costs for twin pregnancies, which mainly result from transferring two embryos after IVF. If only single embryo transfer (SET) would be performed, these extra costs would largely disappear. However, we may also expect that the pregnancy chances of IVF would diminish considerable with SET (van Montfoort *et al.,* 2006).
Our calculations of treatment-independent pregnancy chances were based on data from a waiting list for IVF (Eijkemans *et al.,* 2008) that comprised exposure time up to two years. We assumed that the treatment-independent chances after unsuccessful IVF are the same as for couples who never had IVF. A Danish 5-year cohort study in 818 couples starting assisted reproductive treatment (ART) found that 156 (19%) had delivered from a naturally conceived pregnancy, mostly after start of treatment (134 couples) (Pinborg *et al.,* 2009). Likewise, Cahill *et al.,* 2005, in a three-year follow-up study, found that 18% of couples conceived naturally after unsuccessful IVF.

Just as was found previously by Mol *et al.,* 2000, our results were highly sensitive to the application of a discount rate, particularly at ages around 30. IVF pregnancy chances do not, or only slightly diminish at that age, which means that there is no loss in pregnancy chances when postponing IVF for one year, but that there *is* a saving in costs of unnecessary IVF treatments. Therefore, cost-effectiveness ratio of direct IVF is very high. When discounting future live births and costs, we imply that the preference for a child now would be higher than that of a child next year. A willingness-to-pay study using the direct choice experiment (DCE) method, found evidence of such a preference (Ryan *et al.,* 1999).
Further, it is likely that couples aged over 35 will feel a time pressure, especially when they consider having more than one child.

Figure 4 Duration of infertility at which 'Direct IVF' would become cost-effective in relation to female age and diagnostic category, for various levels of the cost-effectiveness 'willingness to pay' threshold.
In blue: Duration of subfertility at which IVF is indicated for a given age and diagnostic category, according to the Dutch national guideline



We conclude that the duration at which IVF becomes cost-effectives depends, firstly on the level of society's willingness to pay for one extra live birth, and secondly, given a certain level of willingness to pay, on the age of the woman and the diagnostic category.

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Chapter | 12

General discussion
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Summary
Samenvatting
Dankwoord
Curriculum Vitae

General discussion

This final chapter gives answers to the six research questions. The limitations of the findings will be discussed, conclusions will be drawn and recommendations given.

Answers to the research questions:

1. What is the chance of pregnancy for couples starting IVF or ICSI treatment in the Netherlands?

The chance of an ongoing pregnancy was on average 24% after one cycle of IVF or ICSI and 45% after one year since the start of treatment.

A national prospective cohort study was set up to predict the chance of pregnancy for subfertile couples with an indication for IVF or ICSI treatment (chapter 2). There was a loss of 22% of the initially included couples, because 2 IVF centres and 3 transport clinics could not deliver the treatment data. A bias was however unlikely, as the overall yearly treatment results of the centres that did not participate did not deviate from the results of the other centres (see www.lirinfo.nl). In the IVF databases of the participating centres, 15% of the couples were lost due to inexact dates of the start of the first treatment. This loss to follow-up was equally spread over all centres.

The number of embryos transferred per cycle, and the transfers of cryo-preserved embryos were in most centres not recorded. We assumed that a maximum of two embryos were transferred in all centres and that during the study period, the amount of elective single embryo transfers (eSET) were low. The results of cryo-preserved embryos were left out of the analyses for all centres for the reason of comparability.

The relationship of women's age and the pregnancy chance showed a decline after the age of 30, but also a lesser chance for women under 30. This decline in chance in young women was also found in other large datasets (NICE guideline 2004, Templeton *et al.,* 1996). We assumed that child wish at young age could be related to social economic class and lifestyle. On the other hand the decline in chance for women between 40 and 45 was less steep than expected. This could be due to a selection of women with favourable prognostic factors. We recommend further research on in particular this older age group, to improve counselling based on evidence concerning biological predictors instead of solely cut off points by age limits.

The diagnostic category was not of influence on the pregnancy chance. However, it is debatable if unexplained subfertility is a uniform category. It could be a reservoir of couples with different (unexplained) reasons and therefore different chances of pregnancy reflected by e.g. the ovarian reserve capacity. Research on more diagnostic tools to distinct between

good and bad prognosis couples will lead to improvement of the prediction of pregnancy for couples in this category. The higher pregnancy chance with ICSI was most probably attributed to a selection of couples with only severe male, and in most cases no female subfertility. This was demonstrated by the use of ICSI for other than severe male related subfertile couples, for whom ICSI did not improve the pregnancy chance (Bhattacharya *et al.,* 2001).
With the study results we developed a model that can be used in counselling couples about their pregnancy chances with IVF or ICSI in the Netherlands. It is of importance to validate and refine the model with recent data of a complete and more extended national registry. Registration of the full fertility history and pregnancy outcome, including prior fertility treatments as intra-uterine insemination, will be necessary to optimise the prediction of IVF/ICSI outcome.

2. Are there differences in pregnancy chance between IVF centres in the Netherlands?

Differences in pregnancy chance between IVF centres in the Netherlands were present, despite a national IVF guideline, and similarity in experience and size. The adjusted one year ongoing pregnancy chance ranged from 36% to 55%.

The treatment outcomes of the centres obtained from the Dutch national cohort study on pregnancy chance with IVF or ICSI, were compared in chapter 3. Adjustments for patient mix and sampling variability narrowed the differences between centres. However, other patient related predictors, such as lifestyle, ethnicity, and socioeconomic class, were not available, and could be of importance on the IVF/ICSI treatment chance as well.
The pregnancy chance per frozen-thawed embryo transfer, and the number of multiple pregnancies differ between centres. These outcome data could only be obtained for a minority of centres and had to be left out of the analysis for all. During the period of study, double embryo transfer (DET) took place in the majority of all transfers, which enabled the comparison of centres.
We showed differences in pregnancy results between centres which should be researched more extensively after complete registration of all IVF outcome data and registration of more prediction factors, such as lifestyle. We also suggest to look beyond clinical variables, e.g. differences in laboratory procedures.

3. What is the chance of a spontaneous pregnancy when IVF is postponed, and the chance of a spontaneously conceived live birth after termination of IVF treatment?

The average chance of a spontaneous pregnancy when IVF/ICSI treatment would be postponed for one year was 9%. The first year after termination of IVF, the chance of a spontaneously conceived pregnancy was on average 7%.

It is questionable if the waiting list construction was really mimicking postponement of treatment by delay of referral for IVF (chapter 4). The prospect of a treatment on a waiting list, could influence a couple's own attempts of pregnancy. Reversibly, a waiting list could also lead to stress relieve and positively influence the spontaneous pregnancy chance (Evers *et al.,* 1998), although our data did not confirm this assumption.
The average chance of a spontaneous pregnancy on the waiting list was lower compared to the spontaneous pregnancy chance in the most similar study (Collins *et al.,* 1995). An important explanation for this difference can be found in the compliance of all centres to the national guideline for IVF in the Netherlands, which is different from other countries. The guideline restrains couples with still a reasonable chance of a spontaneous pregnancy, by implementing the duration of subfertility per diagnostic category. Furthermore, couples on the waiting list did not succeed with prior, also guideline regulated, conservative treatment options and were therefore a selection of couples with a low chance of a spontaneous pregnancy. This was in contrast with the study of Collins et al., in which the couples had no prior treatment.

The chance of a spontaneously conceived live birth after IVF might have been underestimated (chapter 6), because only the first spontaneous pregnancy was included. Besides, contraceptive use and a period of very low fertility after delivery, because of low frequency of intercourse and cycle recovery, were not reckoned with.
To limit the chance of confounding factors affecting the estimates of a spontaneous pregnancy (e.g. partner change), the follow-up was restricted to 12 months after the last treatment. This method has not been used in the literature, maybe therefore higher chances of pregnancy after termination of IVF were found by others.
The models on the spontaneous pregnancy chance before and after termination of IVF/ICSI, could only distinct the high chance couple from the low in 65% and 66% respectively, of all cases. By adding more prediction factors, e.g. ovarian reserve capacity, pregnancy treatment history, and lifestyle, the ability of the models to predict a spontaneous pregnancy will increase. Couples and professionals should be made aware of the determinants of influence on this chance. It may prevent unnecessary treatment and surprises.

4. What is the impact of lifestyle factors on the pregnancy chance with IVF, and after termination of IVF?

Women who smoke, and women with overweight (BMI ≥ 27 kg/m^2) reduce the live birth rate with IVF treatment by one third. The chance of a spontaneously conceived live birth after termination of IVF treatment was decreased by smoking, overweight, caffeine and alcohol use.

Information on lifestyle factors and pregnancy chance of women who received IVF treatment in the past, were obtained from a historical cohort, the OMEGA-project (chapter 5 and 6).
The relatively high response to the questionnaires (71%), was overrepresented by women who had an IVF child. A lifestyle associated selection bias is however unlikely. Due to limited funding, 24% of all questionnaires were not abstracted. This concerned the medical records of couples of the last hospitals yet to be visited. The loss of questionnaires were therefore not on a patient level, and will not have biased the results on lifestyle and pregnancy chance.
Unfavourable lifestyle factors may have been underreported and the negative effects on the IVF pregnancy rate, or on the spontaneous pregnancy chance after termination of IVF may hold true for actually higher levels of use.
Women and professionals should be conscious of the impact of lifestyle factors on the pregnancy chance during and after termination of IVF. By changing habits women can improve their fecundity throughout the whole fertile live span. The results of lifestyle and the spontaneous pregnancy chance after termination of IVF, suggests that there might also be an adverse effect of caffeine and alcohol on the pregnancy chance with IVF treatment. To clarify the impact of lifestyle factors during fertility treatment, we recommend to register and analyse these patient characteristics in a large scale prospective study.

5. What is the influence of psychological factors on the outcome of IVF? Are emotional problems after unsuccessful IVF treatment predictable?

Anxiety and depression before and during IVF treatment did not lead to a lower pregnancy chance or a higher chance of cancellation of treatment. A screening tool could identify 75% of the women starting a first IVF treatment as being (not) at risk for emotional problems.

In spite of the large number of women included in our study on psychology and subfertility (see chapter 7), lack of power might have been the reason for not finding a relation between patient characteristics (women's age, pregnancy history, cause and duration of subfertility), and IVF pregnancy chance. The same reason might have hold true for the relationship between distress and the IVF pregnancy chance, but our findings were in line with other

prospective studies on baseline and procedural distress and the effect on IVF treatment (Boivin and Takefman, 1995, Klonoff-Cohen *et al.,* 2001, Emery *et al.,* 2003, Anderheim *et al.,* 2005, Smeenk *et al.,* 2005, de Klerk *et al.,* 2008).

Poor prospects of treatment could have been made aware by prior counselling, but this was not reflected in a higher pre-treatment distress level for women with cancelled cycles.

Couples will have their hopes up high and treatment start is often a relieve after "waiting" several years for a pregnancy to occur. The method the fertility problem is communicated, is known to influence the patients' emotional response (Verhaak *et al.,* 2007). Both reassons explain why the average scores of anxiety and depression at pre-treatment were in the normal range of the Dutch Community.

Non-participants had an almost equal subfertility related profile compared to participants. Nevertheless, a bias concerning the distress levels between the two groups cannot be ruled out. Maybe more nervous women were not asked, or had a tendency not to participate, but an opposite reaction on readiness of participation for more distressed women could also hold true.

Lifestyle as smoking, weight, caffeine and alcohol use are known to mediate between fertility and distress, but unfortunately these variables were not added to this study. In future studies lifestyle factors should be involved to create a full picture of psychological state and fertility treatment.

Risk factors for emotional maladjustment were identified by Verhaak *et al* (2005), and incorporated in the questionnaires handed out before and after IVF treatment (chapter 8). SCREENIVF should not be used as a prerequisite for psychological support because of the low positive predictive value (48%) and the limited sensitivity (69%) which could lead to unidentified women with clinical emotional problems. Next to SCREENIVF as a first step in triage, anticipation on deterioration of emotional health is still essential for both patients and professionals. Subsequently, diagnostic investigation and if needed, psychological support can be given to those women who need it the most.

6. What are the costs of an IVF and ICSI treatment in the Netherlands?

The average direct costs of IVF/ICSI treatment were € 10,250 per ongoing pregnancy. The indirect costs, caused by absence from work related to the IVF/ICSI treatment was on average € 600 euros per treatment. The cost-effectiveness ratios per live birth of direct IVF/ICSI compared to postponing treatment with one year were between € 10,000 and € 50,000, depending on women's age, cause and duration of subfertility.

Due to fewer incomplete treatment cycles, lower mean medical costs and higher success rates, the average costs per ongoing ICSI pregnancy were € 250 lower compared to IVF, despite the higher laboratory costs of ICSI (chapter 9). There is however no evidence that ICSI treatments carried out for other causes of subfertility than severe male, will increase pregnancy chances and lower the overall costs.

An embryo transfer with frozen-thawed embryos were double the costs of a fresh embryo transfer, but was only 20% of the costs of a complete IVF/ICSI cycle. Research on improvement of pregnancy chances after cryo preservation, will lead to a decreased physical burden, and higher cost-effectiveness.

The actual costs of a IVF and ICSI treatment may have been underestimated, because wasting costs, were not considered. The diagnostic work-up and costs for counselling preceding a treatment were left aside because of the wide variance between centres. However, we recommend cost-effectiveness research on in particular costs in diagnostic genetics for male related subfertility treated with ICSI.

Differences in health care setting, and heterogeneity of study methods have lead to a low comparability between costs expenditures of IVF and ICSI treatment between European countries. However, the large sized IVF centres in the Netherlands may be the reason for the lower cost estimates compared to the often smaller IVF clinics in other European countries. (Nyboe Andersen *et al.,* 2009).

The response rate to the study on the productivity loss caused by absence from work was only 62%, which is however reasonable considering the 10 week period of completing the daily dairies (chapter 10). Respondents to the study had an embryo transfer in 90% of the cases, which is a high average compared to the national average of 86% reaching embryo transfer in 2003 (www.lirinfo). Under reportage of absence from work could have happened as women with incomplete treatments with no embryo transfer because of fertilisation failure, could have stopped keeping the diary and therefore been overrepresented in the non-responders. Further, results on absence from work were assessed on women having a first IVF or ICSI treatment, but emotional distress and with this, absence from work could increase after more unsuccessful treatments. The higher incidence of twin pregnancies with

IVF treatment and consequently more obstetric complications are likely to increase the absence from work for IVF pregnancies, compared to spontaneous pregnancies. In this study only the first weeks of pregnancy were followed, and absence from work was not significantly different for pregnant women compared to non-pregnant women in the first 8 weeks of gestation.
The explained variance with respect to absence from work of the factors studied (age, hours of work, education level, main reason for absence, and psychological factors), was limited, other, e.g. work-related factors, which we did not study, may have a stronger prediction value on absence from work.
The costs of absence from work for women with physical and/or emotional problems were almost double from the average costs of the IVF related absence from work. We therefore recommend research on prevention of both general and emotional problems with IVF treatment.

The cost-effectiveness of IVF/ICSI for different subgroups of patients was correlated with the spontaneous pregnancy chance and the gain in pregnancy chance with IVF (chapter 11). It was most cost-effective for endometriosis, irrespective of the duration of subfertility and least for unexplained subfertility, because the chance of a spontaneous pregnancy for women in this category was still considerable. It is however questionable if the chance of a pregnancy with, or without treatment, is equal for all couples with unexplained subfertility at a certain age. More research is needed to find out if there are women within this diagnostic category with an extreme low chance of a spontaneous pregnancy, which could be considerably higher with IVF. This study was not conclusive on male subfertility because differentiation between the cost-effectiveness for mild male and severe male subfertility could not be estimated. It is plausible that severe male subfertility, for its low chance of a spontaneous pregnancy and high chance with ICSI, was at least as cost-effective as endometrioses.
The cost calculations include the extra costs for twin pregnancies. When more single embryo transfers are performed, the extra costs will diminish, although the chances of pregnancy with IVF/ICSI will reduce also.
By postponing IVF with one year, more spontaneous pregnancies will occur that would in case of *direct* IVF, be replaced by IVF pregnancies against considerable extra costs. However, this approach will also ignore the preference of a couple to have a pregnancy now instead of next year and restrict a couple in having more children in succession. Further, there is no consensus on the society's willingness to pay for one extra live birth with IVF/ICSI.

Conclusions

1. The pregnancy chance with IVF or ICSI treatment predominantly depends on female age, to a less extend on the duration of subfertility and pregnancy history, and not on the diagnostic category.
2. Differences in success rate between IVF centres in the Netherlands can not be explained by the presently registered patient characteristics.
3. The chance of a spontaneous pregnancy before and after termination of IVF, is dependent on the woman's age, her pregnancy history, the cause and duration of subfertility.
4. Smoking and overweight have a detrimental impact on the pregnancy chance with IVF, and on the spontaneous pregnancy chance after termination of IVF, which is also harmed by caffeine and alcohol use.
5. Anxiety and depression before and during a first IVF/ICSI treatment do not influence the pregnancy chance with IVF.
6. The psychological screening tool "SCREENIVF" can be used as a triage to identify women at risk for emotional problems after IVF/ICSI treatment.
7. Absence from work related to IVF is mainly because of physical and emotional problems due to treatment.
8. The costs of IVF/ ICSI treatment are mainly determined by the costs of medication.
9. The cost-effectiveness of IVF/ICSI treatment depends on the combination of women's age, cause and duration of subfertility.
10. The recommendations of the current IVF guideline are valid, except for unexplained subfertility.

Recommendations

1. The prediction model on pregnancy chances with IVF/ICSI should be validated.
2. Registration of fertility treatment in the Netherlands should be uniform and complete and should include lifestyle.
3. Differences between IVF centres should be studied including more prognostic factors and should not be restricted to clinical variables.
4. Counselling of couples on their chance of a spontaneous pregnancy should be based on prediction models which include lifestyle.
5. A large scale prospective study on lifestyle during fertility treatment should be carried out.
6. Lifestyle factors should be included in research on distress and fertility.
7. The positive predictive value and the sensitivity of the psychological screening instrument "SCREENIVF" should be improved by further research.
8. IVF/ICSI treatment should focus on prevention of physical and emotional problems to reduce absence from work and involved costs.

9. The focus on improvement of the pregnancy chance with IVF/ICSI, should be on progress of the pregnancy chance with frozen-thawed embryo's, to reduce the burden and costs per treatment.
10. More research on the cost-effectiveness of IVF is needed for couples with unexplained subfertility, in particular for women under age 32.

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Summary

In **Chapter 1** the background of the thesis and the study design were outlined. After one year of unprotected intercourse, 15% of all couples do not conceive spontanously. IVF or ICSI treatment can lead to pregnancy and a live birth for some of the involuntary childless couples.

In the Netherlands, IVF exists for more than 25 years and fertilisation with ICSI for more than 15 years. The number of IVF and ICSI treatments has increased every year. At this moment 1 in every 39 children in the Netherlands is an IVF or ICSI child. An important explanation for the rising number of IVF and ICSI treatments is the high mean age at which Dutch women try to conceive their first child. During the optimal fertile period, women give priority to education and their carrier instead of motherhood. With rising women's age the chance of pregnancy decreases and women will appeal to medical treatments more often.

On average, the chance of pregnancy is around 25% per IVF or ICSI cycle. The chance per couple differs and is dependent on known and still unknown factors. It is desirable to predict the chance of success, to save futile treatments, disappointment, risks, and unnecessary costs.

Former research to the factors of influence on the chance of pregnancy have led to the development of the recent IVF guideline, formulated by the Dutch Community of Obstetrics and Gynaecology (NVOG).

The guideline describes when, and after which diagnostic procedures, the indication for IVF and ICSI is reached. Couples with no, or hardly any chance of a spontaneous pregnancy, or after unsuccessful less invasive treatments (e.g. IUI), are referred for IVF. The chance of pregnancy with IVF/ICSI should be weighed up against risks and complications through treatment. The last version of the guideline was written more than 10 years ago and should be updated . Further the evidence for most indications for IVF, according to the guideline should be well-founded.

This thesis addresses six research questions:

1. What is the chance of pregnancy for couples starting IVF or ICSI treatment in the Netherlands?
2. Are there differences in pregnancy rate between IVF centres in the Netherlands?
3. What is the chance of a spontaneous pregnancy when IVF is postponed, and the chance of a spontaneously conceived live birth after termination of IVF treatment?
4. What is the impact of lifestyle factors on the pregnancy chance with IVF, and after termination of IVF?
5. What is the influence of psychological factors on the outcome of IVF/ICSI? Are emotional problems after IVF treatment predictable?

6. What are the costs of an IVF and ICSI treatment in the Netherlands?

Part I (chapter 2-4) of the thesis was mainly based on a prospective cohort study, in which almost all IVF centres in the Netherlands participated. Research question 1, 2 and 3 could be answered with data from this study. We made use of the existing waiting period before IVF/ICSI treatment, which developed because the increasing demand for IVF and ICSI exceeded the supply of treatments per centre. The chance of a spontaneous pregnancy during the waiting period of subfertile couples eligible for IVF treatment, was compared to the chance of pregnancy with treatment for those couples that eventually started IVF/ICSI. Couples were followed from the moment they were on the waiting list up until the first ongoing pregnancy. This is defined as a pregnancy at minimal 8 weeks gestation, with fetal heartbeat demonstrated with sonography. This was applicable for spontaneous, as well as for pregnancies after treatment. Couples on the waiting list were followed until a ongoing spontaneous pregnancy occurred or, in case a spontaneous pregnancy did not occur, until the start of treatment and 12 months there after. The influences of patient characteristics, such as female age, pregnancy history (primary or secondary subfertility), cause and duration of subfertility on the chance of pregnancy were analysed in a prediction model. A comparable prediction model on the chance of a spontaneous pregnancy was developed for couples on a waiting list before treatment. Further, we investigated if there were differences in pregnancy chance per IVF centre.

In part II (chapter 5-8), other determinants on the chance of pregnancy for subfertile couples, such as lifestyle and psychological factors were studied and gave answers to research questions 4 and 5. We used data from the OMEGA-project, a large scale nationwide historical cohort study. This study was initiated in 1995, among women who had at least one IVF treatment between 1983 tot 1995, in one of the IVF centres in the Netherlands. These women were asked to fill in an extensive questionnaire on medical treatments, pregnancies, and lifestyle, before during and after their IVF treatment period. These questionnaires were combined with the medical records. The influences of smoking and the body mass index (BMI) during IVF treatment, and also the influence of caffeine and alcohol use on the spontaneous pregnancy chance after termination of IVF treatment, were assessed.
During the national prospective cohort study on the chance of pregnancy with IVF and ICSI in 7 IVF clinics (3 IVF centres en 4 transport clinics), another research was carried out with validated questionnaires on the influence of psychological factors (anxiety and depression) on the chance of pregnancy and a premature cancellation of treatment. Furthermore, a psychological screening instrument to identify women at risk for psychological damage after unsuccessful treatment was tested.

In part III (chapter 9-11), indirect and direct medical costs of IVF/ICSI treatment were calculated (research question 6). The direct medical costs of an IVF and ICSI treatment were described in detail, using data of 4 IVF centres and 1 transport clinic. The indirect costs of IVF related productivity loss, were assessed in 8 IVF clinics, by combining a diary on absence from work with a psychological questionnaire, to give insight into costs and the factors of influence on the absence from work due to IVF treatment.
Finally, a costs-effectiveness study was carried out by combining the prediction models on the spontaneous pregnancy chance and the chance of pregnancy with IVF/ICSI treatment in relation to the costs of treatment for couples with different patient profiles.

In **Chapter 2** the prognostic values of different patient characteristics used in the Dutch IVF guideline were assessed and evaluated in a model to predict the ongoing pregnancy chance within 12 months after the start of treatment. In a national prospective cohort study, 4928 couples starting IVF or ICSI treatment for the first time between 2002 and 2004, were followed, using the IVF databases of 11 IVF centres and including 20 transport clinics.
The average one-year ongoing pregnancy chance was 45%. Age was identified as the most important predictor of pregnancy, with the highest chance at 30 years of age, and a slight decline for younger and older women. After the age of 35, the pregnancy chance dropped more steep. The chance of pregnancy for women around 40 were half the chance of women of 30 years of age. Couples with severe male subfertility treated with ICSI had a 22% higher chance of an ongoing pregnancy than couples in the other diagnostic categories treated with IVF. The chance of pregnancy for women with a pregnancy history was on average 10 % higher compared to women with primary subfertility. The results also showed that with a longer duration of subfertility the chance of pregnancy decreased with 3% every year.
In this study we developed a model for the prediction of pregnancy with IVF or ICSI. The prognostic factors mentioned can be used to counsel individual couples about their chance of pregnancy at the start of a first treatment.

In **Chapter 3** we investigated if the differences in the one year ongoing pregnancy chance between IVF centres remained after adjustment for patient mix. For this study we used prospectively collected IVF and ICSI treatment data, see also chapter 2, and separated the outcomes per centre. Adjustment for differences in patient mix per centre was carried out by implementing the prognostic index which included the subfertility related factors: age, pregnancy history, cause and duration of subfertility, and which was obtained from the model in chapter 2.
The crude one year ongoing pregnancy chance was compared to the mean of all centres and differed nearly a factor 3 between centres. Accounting for sampling variation the range shrank to a factor 2. After adjustment for patient mix the range narrowed a little further. One

year after the start of treatment, the adjusted ongoing pregnancy chance differed between 36% and 55% in the two utmost centres.
Only17% of the variation between centres could be explained by the differences in patient mix, as registered in the IVF databases. Further research is needed to elucidate the causes of the remaining differences.

In **Chapter 4** we estimated the chance of a spontaneous pregnancy for IVF and ICSI patients, using data on the waiting list before the start of treatment. In a prospective cohort study with a duration of two years, we included 5962 couples, registered on a national waiting list before IVF or ICSI. The waiting list data were matched with the IVF/ICSI registries of the IVF centres that participated to the study (see chapter 2). For the couples that did not match, the medical files were searched by hand. The patient characteristics of the couples that had not started IVF/ICSI because of the occurrence of a spontaneous pregnancy while on the waiting list, were determined and used in the analysis. The prediction of a spontaneous pregnancy was assessed while considering female age, the duration of subfertility, pregnancy history, and the diagnostic category.
The cumulative probability of a spontaneous ongoing pregnancy on a waiting list before the start of IVF or ICSI was 9% at 12 months. For less than 10% of the couples this chance was more than 15%. The chance of a spontaneous pregnancy decreased with 5% with every year increase of women's age, with 15% per year increase in the duration of subfertility, and with 29% for primary, compared to secondary subfertility. All diagnostic categories showed higher chances of a spontaneous pregnancy compared to tubal pathology. For couples with unexplained subfertility this chance was even 2,6 times higher.
The chance of an ongoing spontaneous pregnancy while waiting for an IVF treatment was on average below 10% but maybe as high as 25% within one year for couples with only favourable prognostic factors.

In **Chapter 5** the separate and combined effects of subfertility related factors and the lifestyle factors smoking and BMI on the live birth rate with IVF were studied on women who had a first IVF treatment in one of the IVF centres in the Netherlands during 1983 and 1995. Information on lifestyle and pregnancy outcome was retrospectively obtained from questionnaires filled in by 8457 women and combined with their medical records (the OMEGA-project).
In those days, the overall live birth rate per cycle was 15%. With increasing female age the overall live birth rate decreased with 2% with every year increase. Multivariate analysis revealed that the chance of an IVF live birth decreased with 28% for smokers. Women with overweight (BMI $\geq$ 27 kg/m^2), had a 33% lower chance of an IVF live birth compared to normal weight women (BMI $\geq$ 20 and $<$ 27 kg/m^2). Couples with male subfertility had a 30% lower chance of a live birth with IVF treatment compared to the other two diagnostic categories

defined (tubal pathology and other subfertility reasons). The duration of subfertility and the pregnancy history before the start of the first IVF did not influence the live birth rate.
This research with historical data on IVF treatment in the Netherlands revealed the average chance of a live birth with IVF between 1983-1995, and gained insight into the influences of subfertility related factors and lifestyle on that chance.

In **Chapter 6** we predicted the chance of a spontaneous conception leading to a live birth after termination of successful and unsuccessful IVF treatments, based on subfertility related factors and lifestyle. The historical OMEGA-cohort (see also chapter 5), of 8669 women who received at least one IVF treatment were used, the follow-up interval after last IVF treatment was on average 5 years.
Within the first year after last IVF, or within a year after the delivery of an IVF live birth, the chance of a spontaneous conception which led to a live birth was 7%. The chance decreased with 6% with every year increase of women's age. There was a differerence in effect of the variables of influence on the chance of a spontaneous pregnancy for couples with, and without an IVF-child after last IVF. For couples with an unsuccessful last IVF the chance of a spontaneously conceived live birth decreased with 20% after more than 6 year duration of subfertility, and with 29% after more than 4 IVF attempts. Smoking decreased the chance with 28%, for women with a BMI higher than 27 kg/m^2 the chance decreased with 53%, for caffeine use of more than 4 units per day with 28% and with 43% when more than 3 units of alcohol per week were used.
The influence of subfertility related factors and lifestyle on the chance of (spontaneous) pregnancy for subfertile couples before and during IVF, also applied for the spontaneous conception chance after termination of IVF.

In **Chapter 7** we performed a multicentre prospective cohort study in 783 women starting a first IVF or ICSI treatment, to assess the influences of anxiety and depression on the pregnancy rates. Additionally, we studied the effect of anxiety and depression on the chance of premature cancelation of an IVF treatment. We also determined if a change in anxiety level from pre-treatment to just before oocyte retrieval, affects the pregnancy rate. Anxiety and depression levels were assessed by a validated questionnaire containing the short versions of the State Anxiety Inventory (STAI) and Beck Depression Index-Primary Care (BDI-PC). Results from the questionnaires were combined with the treatment outcomes from the IVF registries obtained from the national cohort study (see chapter 2). The predictive values of distress were assessed while controlling for women's age, pregnancy history, duration and cause of subfertility.
Neither anxiety, depression, nor a rise in anxiety during treatment, had an effect on the pregnancy rate. The cancellation rate was also not affected by the pre-treatment anxiety and depression levels.

Inductees in IVF/ICSI treatment can be reassured about the influence of distress on the chance of pregnancy.

In **Chapter 8** we investigated the psychometric characteristics of a screening tool to identify women, before treatment, who are at risk to develop emotional problems caused by IVF/ICSI. Risk factors for emotional maladjustment were determined in a previous study and incorporated in a questionnaire. "SCREENIVF" was handed out at pre-treatment (see also chapter 7), and 6 weeks after oocyte retrieval, and was studied in 279 women.
SCREENIVF successfully identified 75% of the women at risk, or not at risk for emotional maladjustment. The sensitivity of the test was 69%, meaning that 69% of the women with emotional problems after the first treatment indeed were identified by the test. negative predictive value was high (89%), but the positive predictive value of SCEENIVF was low: only 48% of the women testing positive on risk factors indeed had clinical signs of emotional problems.
SCREENIVF can be used as a triage instrument and a tool to anticipate on the risk profile of women starting IVF. Subsequently, detailed diagnostic interviews, possibly followed by psychological treatment could prevent drop-out of treatment or deterioration of psychological wellbeing.

In **Chapter 9** the productivity loss and the pattern of absence from work due to a first IVF/ICSI treatment was assessed. Additionally, the influences of general and psychological variables on the absence from work were analysed. In a prospective multicentre cohort study the costs of IVF related absence from work was derived from a diary kept by 384 women, from the start of treatment up until 10 weeks thereafter. Women filled in a psychological questionnaire at pre-treatment (see also chapter 7) and at closure of the diary. The treatment results of these women were obtained from the national cohort study on the prediction of IVF /ICSI treatment (chapter 2).
On average, women had 33 hours of absence from work during the 10 weeks registered. The overall absence from work due to IVF/ICSI treatment was 23 hours per first cycle, which was a productivity loss due to the treatment of almost € 600. The main reason for absence from work was for half of all women physical and/or emotional problems. The average productivity loss for women with complaints were 4 times higher than for the other women who registered hospital visits as the main reason for absence from work, which was on average 10 hours. Absence from work was positively correlated with the hours of paid work and with physical or emotional complaints. Women with a high education level had a lower average of absence from work compared to a secondary education level. To reduce the costs due to absence from work we should focus on prevention of physical and emotional problems.

In **chapter 10** the costs of a first IVF and ICSI treatment up until an ongoing pregnancy were described per stage of treatment and per treatment with frozen-thawed embryos. Detailed information about the costs of a first IVF and ICSI treatment were obtained in 4 IVF centres and 1 transport clinic. The treatment results were derived from the IVF registrations from the national cohort study (see chapter 2), from the annual reports of three IVF centres, and from the national infertility registration (LIR).

The costs of a first IVF or ICSI cycle were on average almost € 2500. The costs of an ICSI treatment were on average 8% higher compared to an IVF cycle, due to the higher specific equipment costs and labour-intensive procedures. Per ongoing pregnancy the costs with ICSI were on average lower compared to IVF, because of a higher chance of success with ICSI. The cost for medication covered the major part of the treatment costs. From 34 years onward, the total costs per ongoing pregnancy increased because of a higher mean dosage of follicular stimulating hormone used and a lower mean chance of pregnancy. The costs of preservation, thawing and transfer of cryo-preserved embryos were on average € 550 per treatment.

Based on the number of treatments from the LIR data in 2004 and the average ongoing pregnancy rates after IVF, ICSI, and cryo-transfers, the costs per ongoing pregnancy resulted from IVF or ICSI were around € 10,250.

In **Chapter 11** we aimed to establish the cost-effectiveness comparison between starting IVF/ICSI according to the IVF guideline as used in the Netherlands ("direct-IVF"), and waiting one more year before the start of treatment. The prediction model on the pregnancy chance one year after the start of IVF/ICSI (see chapter 2), and the prediction model on the spontaneous pregnancy chance on a national waiting list before treatment (see chapter 4), were used for comparison of effectiveness. Costs of treatment were determined from couples starting IVF/ICSI (see chapter 10). The total costs of the treatment per live birth were added to the costs of subsequent delivery and neonatal care. The costs and the percentage of multiple births with IVF/ICSI were reckoned with. Analyses were carried out for women with different diagnostic categories, age and duration of subfertility.

The cost-effectiveness ratio is the difference in costs per live birth with direct IVF compared to the costs of postponing IVF with one year, divided by the difference in chance of a live birth between the two scenario's. The cost-effectiveness ratios were between € 10,000 and € 50,000 per live birth. For women with endometriosis the cost-effectiveness ratio was just below € 10,000 from 34 years onward. For all other diagnostic categories, regardless off age, the cost-effectiveness ratio is higher. For women with unexplained subfertility the ratio was € 30,000 from age 32 onward and 3 year duration of subfertility.

In conclusion, postponement of IVF will save costs against a small loss in overall live birth rate. The cost-effectiveness of IVF is dependent on the diagnostic category, on woman's age, and the duration of subfertility, but also on the society's willingness to pay for an extra live birth.

In **chapter 12** the answers to the research questions, the main conclusions and recommendations are given:

1. In the Netherlands, the chance of an ongoing pregnancy was on average 24% after one cycle of IVF or ICSI and 45% after one year since the start of treatment. The pregnancy chance with IVF or ICSI treatment is mainly dependent on the female age, partly on the duration of subfertility and pregnancy history, and not at all on the cause for IVF. The prediction model on pregnancy chance with IVF/ICSI should be validated with a national uniform registration of fertility treatment and include lifestyle.

2. The adjusted one year ongoing pregnancy chance between IVF centres in the Netherlands ranged from 36% to 55%. Patient mix explains these differences for only a small part. To elucidate the differences between centres, more clinical and non-clinical variables should be registered and included in research.

3. The average chance of a spontaneous pregnancy when IVF/ICSI treatment would be postponed for one year was 9%. The first year after termination of IVF, the chance of a spontaneous pregnancy was on average 7%. Both before and after termination of IVF, the chance of a spontaneous pregnancy, is dependent on the woman's age, her pregnancy history, the cause and duration of subfertility. Counselling of couples on their chance of a spontanous pregnancy should be based on prediction models including lifestyle.

4. Women who smoke, and women with overweight (BMI ≥ 27 kg/m^2) reduce the live birth rate with IVF treatment by one third. The chance of a spontanously conceived live birth after termination of IVF treatment was decreased by smoking, overweight, caffeine and alcohol use. Lifestyle factors during fertility treatment should be prospectively studied on a large scale.

5. Anxiety and depression before and during IVF treatment did not lead to a lower pregnancy chance or a higher chance of cancellation of treatment. "SCREENIVF" could identify 75% of the women starting a first IVF treatment as being (not) at risk for emotional problems after treatment.
The sensitivity of the psychological screening instrument should be improved. Further research on distress and fertility should include lifestyle factors.

6. The average direct costs of IVF/ICSI treatment were € 10.250 per ongoing pregnancy.
The indirect costs, caused by absence from work related to the IVF/ICSI treatment was on average € 600 euros per first cycle. By prevention of physical and emotional problems during

IVF/ICSI treatment, the costs of absence from work due to IVF treatment can be importantly lowered.

For women over 32 years of age of all diagnostic categories, the cost-effectiveness ratios of direct IVF compared to postponement was between € 10,000 and € 25,000 per live birth. Except for women with unexplained subfertility. Unless they would wait at least one other year on top of the recommended three years of the current guideline IVF.

Samenvatting

Hoofdstuk 1

Achtergrond, doelen en de onderzoekspopulaties

Zwanger worden via de natuurlijke weg is voor ongeveer 15% van alle paren een probleem. Een IVF of ICSI behandeling kan voor sommige ongewenst kinderloze paren een oplossing bieden. Bevruchting via IVF bestaat in Nederland inmiddels ruim 25 jaar, middels ICSI al meer dan 15 jaar. Het aantal IVF en ICSI behandelingen dat per jaar wordt uitgevoerd neemt nog steeds toe. Op dit moment is 1 op de 39 kinderen in Nederland een IVF of ICSI kind. Een verklaring voor de stijgende behoefte aan IVF en ICSI heeft te maken met het uitstellen van de kinderwens. Tijdens de optimaal vruchtbare periode geven veel vrouwen de voorkeur aan het volgen van een opleiding en de ontwikkeling van een carrière om sociaal/maatschappelijke en economische redenen. Naarmate een vrouw ouder wordt, dalen echter haar kansen op een zwangerschap en zal zij vaker een beroep doen op de medische mogelijkheden om deze kans te vergroten.

Met de ontwikkelingen in de voortplantingsgeneeskunde is de kans van slagen per behandeling in de loop der jaren toegenomen. Voor alle vormen van kunstmatige bevruchting ligt de gemiddelde kans op zwangerschap rond de 25% per behandeling. De kansen per paar zijn verschillend en afhankelijk van een aantal bekende, maar ook nog steeds onbekende factoren. Het is wenselijk om een zo goed mogelijke voorspelling van de slaagkans te kunnen doen, om vergeefse behandelingen, teleurstelling en risico's te voorkomen en onnodige kosten te besparen.

Eerder onderzoek naar de factoren van invloed op de kans op zwangerschap hebben geleid tot de ontwikkeling van de huidige richtlijn IVF geformuleerd door de Nederlandse Vereniging voor Obstetrie en Gynaecologie (NVOG). De richtlijn beschrijft op welk moment en na welke diagnostische procedures, er een indicatie bestaat voor een behandeling IVF en ICSI, met als doel de paren die via de natuurlijke weg, of na minder invasieve methodes van behandeling (bijvoorbeeld intra uterine inseminatie, IUI) geen, of weinig kans maken op een zwangerschap, te verwijzen voor behandeling. De kans op een zwangerschap door IVF/ICSI dient daarbij ook afgewogen te worden tegen de kansen op een complicatie door behandeling. De laatste versie van de richtlijn bestaat inmiddels ruim 10 jaar en is toe aan herziening. Daarbij zou de richtlijn voor de meeste indicaties wetenschappelijk beter onderbouwd kunnen worden.

Dit proefschrift behandelt zes onderzoeksvragen:

1. Wat is de kans op zwangerschap voor paren die een IVF of ICSI behandeling ondergaan in Nederland?
2. Zijn er verschillen in kans op zwangerschap tussen de IVF centra in Nederland?
3. Wat is de kans op een spontane zwangerschap indien IVF één jaar langer zou

worden uitgesteld en de kans op een spontane zwangerschap nadat IVF is afgesloten?
4. Wat is de invloed van levensstijl factoren op de kans op zwangerschap met IVF en de kans op een spontane zwangerschap nadat IVF is afgesloten?
5. Wat is de invloed van psychologische factoren op de uitkomst van IVF/ICSI? Zijn emotionele problemen die kunnen ontstaan na IVF te voorspellen?
6. Wat zijn de kosten van IVF en ICSI in Nederland?

Opbouw proefschrift:
In deel I van dit proefschrift (hoofdstuk 2-4), werd de kans op een zwangerschap voor paren die volgens de richtlijn IVF in aanmerking kwamen voor een behandeling IVF of ICSI berekend. De invloed van verschillende patiënt karakteristieken: de leeftijd van de vrouw, de aard van de subfertiliteit (primaire of secundair), de oorzaak (diagnostische categorie) en duur van de fertiliteitstoornis werden meegewogen in een kansmodel. Deze paren stonden vóór behandeling op een wachtlijst. Voor de kans op een spontane zwangerschap in de wachttijd voor IVF werd eveneens een predictie model gemaakt.
Paren verschillen in kans op zwangerschap, of er ook verschillen bestaan in de kans op zwangerschap per IVF centrum is eveneens onderzocht.

In deel II (hoofdstuk 5-8), werden andere factoren die de kans op een zwangerschap kunnen beïnvloeden onderzocht. De invloed van psychologische ("stress"), en levensstijlfactoren zoals roken, overgewicht, cafeïne- en alcohol gebruik op de kans op zwangerschap voor, tijdens en na IVF/ICSI werden bestudeerd. Tevens hebben we onderzocht of voortijdige herkenning van vrouwen die mogelijk psychische schade ondervinden van een behandeling mogelijk was.

In deel III van het proefschrift (hoofdstuk 9-11), werden de kosten van een IVF/ICSI behandeling en de doelmatigheid, oftewel de kosten-effectiviteit van een behandeling bepaald. De direct medische kosten werden berekend en de indirect medisch kosten ten gevolge van productiviteitsverlies door werkverzuim werden onderzocht. De kosteneffectiviteit analyse werd uitgevoerd voor paren in verschillende diagnostische categorieën, waarbij de duur van de vruchtbaarheidsstoornis en leeftijd van de vrouw werden meegewogen.

Een prospectief cohort onderzoek, waaraan vrijwel alle IVF centra in Nederland hebben deelgenomen, vormt de basis voor dit proefschrift. Alle paren in dit onderzoek hadden een verwijzing voor behandeling IVF of ICSI. Ten tijde van het onderzoek bestond door de toenemende vraag naar behandelingen en een beperking in het aantal behandelingen per IVF centrum, bij vrijwel alle klinieken een wachttijd vóór behandeling. Om de effectiviteit van

IVF te beoordelen, werd de kans op een spontane zwangerschap in de wachtperiode voor IVF vergeleken met de kans op zwangerschap met IVF/ICSI, voor die paren die uiteindelijk gingen starten met een behandeling. Paren werden gevolgd vanaf het moment dat ze op de wachtlijst werden geplaatst tot aan de eerste "doorgaande" zwangerschap. Dat betekent een zwangerschap van 8 weken na de laatste menstruatie, waarbij echografisch hartactie is geconstateerd. Dit gold zowel voor de spontane zwangerschap als voor de zwangerschap ontstaan na behandeling.

Voor de invloed van levensstijlfactoren op de kans op zwangerschap tijdens en ná IVF is gebruik gemaakt van het OMEGA-gegevensbestand. Het OMEGA-project is gestart in 1995: vrouwen die vanaf 1983 tot 1995 IVF ondergingen in Nederland, konden een uitgebreide vragenlijst invullen over medische behandelingen, zwangerschappen en levensstijl factoren vóór, tijdens en na de IVF periode. De vragenlijst gegevens werden gecombineerd met de gegevens uit de medische dossiers.

Gedurende het nationale prospectief cohort onderzoek naar de kans op zwangerschap met IVF en ICSI werd er in 7 IVF klinieken (3 IVF centra en 4 transportklinieken), tevens een prospectief onderzoek gestart met gevalideerde vragenlijsten naar de invloed van psychologische factoren (angst en depressie) op de kans op zwangerschap en het voortijdig afbreken van een behandeling. Bovendien is het onderscheidend vermogen van een nieuw ontwikkelde psychologische vragenlijst getest. De vraag was of vrouwen met een hoog risico op psychische schade na een behandeling, voorafgaand aan de behandeling geïdentificeerd kunnen worden met de test. Tenslotte diende de vragenlijst inzicht te geven in de invloed van fysieke en emotionele problemen op het ziekteverzuim.

De kosten van een IVF en ICSI behandeling zijn gedetailleerd in kaart gebracht. Met deze gegevens en met de gegevens van het predictie model betreffende de kans op spontane zwangerschap en het model over de kans op zwangerschap met IVF of ICSI, is een kosten-effectiviteits analyse van een behandeling IVF/ICSI verricht per diagnostische categorie. Op grond van de leeftijd van de vrouw en de duur van het vruchtbaarheidsprobleem zouden met deze gegevens een nieuwe richtlijn IVF ontwikkeld kunnen worden.

Hoofdstuk 2

Kans op zwangerschap met IVF of ICSI

In dit hoofdstuk werd de voorspelling van de kans op een doorgaande zwangerschap binnen één jaar vanaf de start van een eerste behandeling IVF of ICSI onderzocht. De voorspellende waarde van verschillende patiënt karakteristieken werd berekend met behulp van een predictie model. De gegevens voor dit onderzoek zijn verkregen tijdens een nationale prospectieve cohort studie uitgevoerd tussen 2002 en 2004. Van 11 van de 13 IVF centra en 20 van de 23 transportklinieken in Nederland zijn de behandelgegevens van in totaal 4928 paren gebruikt

Binnen 1 jaar na start van de behandeling IVF of ICSI was de kans op een doorgaande zwangerschap gemiddeld 45%. De volgende determinanten zijn gebruikt in het model: de leeftijd van de vrouw, de diagnostische categorie, of te wel de indicatie voor behandeling, de duur en de aard van de subfertiliteit (primair of secundair). De leeftijd van de vrouw was de belangrijkste voorspeller van de kans op zwangerschap. Met het stijgen van de leeftijd van de vrouw nam de kans op zwangerschap af. De hoogste kans lag rond de 30 jaar en er was een lichte afname in kans voor zowel jongere als voor oudere vrouwen tot 35 jaar, daarna daalde de kans op zwangerschap sterker. Voor vrouwen rond de 40 bleek de kans op zwangerschap slechts de helft van de kans ten opzichte van vrouwen rond de 30 jaar. De grootste kans van slagen lag bij paren die behandeld werden met ICSI vanwege ernstig verminderde zaadkwaliteit. Zij hadden 22% meer kans van slagen binnen 1 jaar na de start van behandeling in vergelijking tot paren die behandeld werden met IVF. Dit was onafhankelijk van de indicatie voor IVF. Vrouwen die al eerder zwanger waren geweest hadden 10% meer kans op een doorgaande zwangerschap met IVF/ICSI dan vrouwen met een primaire subfertiliteit. Hoe langer de duur van de subfertiliteit, des te kleiner de kans op zwangerschap, per jaar nam de kans met 3% af.

Met bovenstaande gegevens is een model ontwikkeld, waarmee de individuele kans van slagen met behulp van de verschillende patiëntkarakteristieken voor een paar berekend kan worden.

Hoofdstuk 3

Verschillen tussen IVF klinieken in Nederland

In dit hoofdstuk was onderzocht of er verschillen bestaan in de kans op een doorgaande zwangerschap met IVF of ICSI tussen de verschillende IVF centra in Nederland nadat gecorrigeerd was voor de verschillen tussen de patiënten per centrum. De prospectief verzamelde gegevens van 11 centra, zie hoofdstuk 2, zijn hiervoor gebruikt. De prognostische index factor (een maat voor de invloed per voorspellende factor op de zwangerschapskans), verkregen vanuit het model in hoofdstuk 2, was gebruikt om voor de verschillen tussen de patiënten per kliniek te corrigeren. Tevens is rekening gehouden met de variatie in steekproef. Per IVF centrum was het absolute verschil in doorgaande zwangerschapskans, één jaar na start van de behandeling, vergeleken met de gemiddelde kans van alle centra.

De ruwe zwangerschapskansen verschilden een factor 3 tussen de centra. Na aanpassing aan de variatie in steekproef per centrum nam het verschil in zwangerschapkans tussen de twee uiterste centra af tot een factor 2. Bij een derde vergelijking is gecorrigeerd voor de indexfactor, waarbij er rekening werd gehouden met de leeftijd van de vrouw, of ze ooit eerder zwangerschap was geweest (primaire dan wel secundaire subfertiliteit), de duur van de fertiliteitstoornis en de diagnostische categorie. Hierdoor werd het verschil tussen de centra nog wat kleiner. Een jaar na de start van de behandeling, bedroeg de aangepaste en

gecorrigeerde kans op een doorgaande zwangerschap voor de twee uiterste centra 36% en respectievelijk 55%.
Slechts 17% van het verschil in zwangerschapskans tussen de centra kon worden verklaard door de verschillen in de geregistreerde patiënten karakteristieken. De overige redenen die de verschillen zouden kunnen verklaren dienen verder onderzocht te worden.

Hoofdstuk 4

Zwangerschapskans op de wachtlijst vóór IVF of ICSI

In dit hoofdstuk werd een model weergegeven dat de kans op een spontane zwangerschap in de wachttijd vóór IVF of ICSI voorspelt. Alle paren die voor IVF of ICSI in aanmerking kwamen in één van de deelnemende IVF centra werden gedurende twee jaar prospectief gevolgd vanaf het moment dat ze op wachtlijst stonden. Hierna vond een koppeling plaats tussen de paren op de wachtlijst met de paren van de IVF registraties van de verschillende klinieken. Van de paren die niet in de IVF registraties gevonden werden, maar die wel op de wachtlijst stonden, werd vanuit de medische dossiers onderzocht wat de reden van het uitblijven van een behandeling was. De invloed van de factoren: leeftijd van de vrouw, de oorzaak, de duur en de primaire dan wel secundaire subfertiliteit op de kans op een spontane zwangerschap gedurende de wachttijd vóór IVF, werden in een predictie-model weergegeven.
De cumulatieve kans op een doorgaande spontane zwangerschap in de wachttijd voor IVF, indien de behandeling IVF of ICSI 1 jaar zou worden uitgesteld was gemiddeld 9%. Minder dan 10% van alle paren op de wachtlijst had een kans die groter was dan 15%. Per jaar leeftijdsstijging nam de kans op een spontane zwangerschap bij uitstel van de behandeling met 5% af. Met ieder jaar dat de fertiliteitstoornis langer duurde, nam de kans met 15% af. Ook de diagnostisch categorie was van invloed. Voor paren met een onbegrepen fertiliteitstoornis was de kans 2,6 maal groter dan voor paren verwezen vanwege tubapathologie. Vrouwen die niet eerder zwanger waren, hadden bijna 30% minder kans om alsnog spontaan zwanger te worden in de wachttijd vóór een behandeling in vergelijking met secundair subfertiele vrouwen.
Gemiddeld genomen was de kans op een spontane zwangerschap binnen 1 jaar nadat de indicatie voor IVF of ICSI was bepaald, minder dan 10%, maar deze kon oplopen tot 25% voor vrouwen met de meest gunstige voorspellende factoren.

Hoofdstuk 5

Factoren van invloed op de zwangerschapskans met IVF

Dit hoofdstuk presenteerde de invloed van de patiëntkarakteristieken gerelateerd aan de verminderde fertiliteit, op de kans op een levend geborene na een eerste IVF behandeling. Tevens werd de invloed op de kans op zwangerschap met IVF van deze patiëntkarakteristieken gecombineerd met roken en de BMI. De verzamelde gegevens over levensstijl en zwangerschaps-

uitkomsten werden verkregen uit een vragenlijst die werd gebruikt bij het OMEGA-project zie hoofdstuk 1. De onderzoekspopulatie bestond uit 8.457 vrouwen die tussen 1983 en 1995 minimaal één IVF behandeling hadden ondergaan in één van de destijds 12 IVF centra in Nederland.
De gemiddelde kans op een levendgeborene in die periode was 15% per gestarte IVF cyclus. Met het stijgen van de leeftijd van de vrouw nam de kans op een levendgeborene na IVF af met 2% per jaar. De onafhankelijke invloed van meerdere variabelen is onderzocht: Over het algemeen hadden rokers 28% minder kans op een levend geborene en een significant hogere kans op een miskraam in vergelijking met niet-rokers. Vrouwen met overgewicht (BMI ≥ 27 kg/m^2), hadden 33% minder kans dan vrouwen met een normaal gewicht (BMI 20-27 kg/m^2). De paren die IVF ondergingen vanwege een verminderde kwaliteit zaad hadden 30% minder kans op een levendgeborene per eerste cyclus, in vergelijking met paren in twee andere diagnostische groepen (tubapathologie of overige oorzaken voor subfertiliteit). De duur van de fertiliteitstoornis en een eventuele zwangerschap in het verleden waren niet van invloed op de kans op een levendgeborene met IVF.
Dit onderzoek over de eerste periode van IVF in Nederland gaf inzicht in de gemiddelde kans van slagen met IVF destijds, waarbij de invloed van aan subfertiliteit gerelateerde factoren en levensstijl factoren op de kans op een levendgeborene is bepaald.

Hoofdstuk 6

Kans op een spontane zwangerschap ná stoppen met IVF

We onderzochten de kans op een levend geborene, ontstaan uit een spontane zwangerschap, na afsluiting van de laatste IVF behandeling. De studie is uitgevoerd onder 8.669 vrouwen die in het verleden één of meerder IVF behandelingen hebben ondergaan (OMEGA-project, zie ook hoofdstuk 5) en die tot gemiddeld 5 jaar na de laatste IVF behandeling gevolgd zijn.
Binnen één jaar na het afsluiten van IVF, of binnen 1 jaar na de geboorte van een IVF kind, kreeg 7% van de vrouwen alsnog een kind via spontane conceptie. De kans op een spontane zwangerschap was afhankelijk van de oorzaak van de fertiliteitstoornis. Met het stijgen van de leeftijd van de vrouw nam de kans op een kind via spontane conceptie met 6% per jaar af. Er waren verschillen in het effect van de onderzochte factoren van invloed op de kans op een spontane zwangerschap voor paren die middels de laatste IVF een kind hadden gekregen, in vergelijking met paren die daarbij geen IVF-kind kregen. Voor paren met een niet succesvolle laatste IVF behandeling daalde de kans op een spontane zwangerschap met 20% indien de fertiliteitstoornis langer dan 6 jaar bestond en daalde met 29% indien vooraf meer dan 4 IVF pogingen hadden plaatsgevonden. Roken verlaagde de kans met 28%, overgewicht (BMI ≥ 27 kg/m^2) met 53%, cafeïne (≥ 4 koppen koffie per dag), deed de kans met 28% dalen en alcohol (≥ 3 glazen per week) verkleinde de kans met 43%.
De invloed van de onderzochte factoren op de zwangerschapskans vóór en tijdens IVF bleek ook te gelden voor de kans een spontane zwangerschapskans ná stoppen met IVF.

Hoofdstuk 7

Invloed van angst en depressie op de kans op zwangerschap met IVF/ICSI

In een prospectieve studie werd de invloed van angst en depressie op de kans op zwangerschap met IVF/ICSI en de kans op het voortijdig staken van een behandeling onderzocht. Dit onderzoek werd uitgevoerd onder 783 vrouwen in 7 IVF klinieken tijdens een eerste IVF/ICSI behandeling. Voorafgaand aan de behandeling en kort vóór de punctie vulden zij een gevalideerde psychologische vragenlijst in. De uitkomsten van de vragenlijsten werden gecombineerd met de uitkomsten van de behandelingen, verkregen via de nationale cohort studie beschreven in hoofdstuk 2. De voorspellende waarde van angst en depressie werd berekend, nadat voor meerdere variabelen die de kans op een zwangerschap kunnen beïnvloeden (leeftijd van de vrouw, diagnostische categorie, primaire, dan wel secundaire subfertiliteit en de duur van de fertiliteitstoornis), werd gecorrigeerd.

Angst en depressie voorafgaande aan een behandeling hebben geen invloed op de kans op zwangerschap en evenmin op de kans op een voortijdig afgebroken cyclus. Angststijging kort voor de eicel punctie, ten opzichte van het angst niveau enkele weken vóór de start van de behandeling, heeft eveneens geen invloed op de kans op zwangerschap.

Vrouwen die een eerste behandeling IVF/ICSI ondergaan kunnen gerustgesteld worden, hun gemoedstoestand heeft geen invloed op de kans op zwangerschap.

Hoofdstuk 8

Risico op emotionele problemen na IVF of ICSI.

In dit hoofdstuk wordt beschreven of vrouwen met een verhoogd risico op het ontwikkelen van emotionele problemen na IVF/ICSI, voorafgaand aan de behandeling geïdentificeerd kunnen worden. Risicofactoren voor het ontwikkelen van emotionele problemen werden vastgesteld in een eerdere studie en opgenomen in een vragenlijst. "SCREENIVF" werd voorafgaande aan eerste IVF/ICSI en 6 weken na de punctie van een behandeling afgenomen bij 279 vrouwen.

Het bleek dat 75% van de vrouwen juist geïdentificeerd kunnen worden op het al dan niet krijgen van emotionele problemen. De sensitiviteit van de test was 69%, dit betekent dat 69% van de vrouwen die uiteindelijk emotionele problemen kregen met de test konden worden geïdentificeerd. De negatief voorspellende waarde van de test was hoog (89%), echter de positief voorspellende waarde was laag. Slechts 48% van de vrouwen met een, volgens SCREENIVF risicoprofiel, hadden inderdaad klinisch meetbare emotionele problemen.

SCREENIVF kan gebruikt worden als een triage instrument en als hulpmiddel om te anticiperen op het risicoprofiel van vrouwen die starten met IVF. Vervolgens zou proactieve psychologische diagnostiek en begeleiding kunnen plaatsvinden ter preventie van voortijdige uitval of achteruitgang van psychisch welzijn.

Hoofdstuk 9

Kosten en oorzaken van werkverzuim tijdens IVF/ICSI

De kosten van werkverzuim veroorzaakt door een eerste IVF/ICSI behandeling werden bepaald en de invloed van fysieke en de psychische klachten op het werkverzuim werd geanalyseerd. Het aan de IVF behandeling gerelateerde werkverzuim werd met behulp van een dagboekje bijgehouden door 384 vrouwen die werden behandeld in 8 verschillende IVF klinieken in Nederland. Voorafgaande aan de behandeling vulden zij ook een psychologische vragenlijst in (zie hoofdstuk 7). De uitkomsten van de behandelingen zijn verkregen uit de nationale cohort studie (zie hoofdstuk 2).

Gemiddeld genomen was het werkverzuim 33 uur; 23 uur daarvan was gerelateerd aan de IVF/ICSI behandeling. Dit betekent een productiviteitsverlies door de IVF/ICSI behandeling van circa € 600 per behandeling. De belangrijkste reden voor het werkverzuim was voor 50% van de vrouwen fysieke en/of psychische klachten door de behandeling. Voor deze vrouwen waren de kosten voor het productiviteitsverlies het 4-voudige ten opzichte van de overige vrouwen die voornamelijk verzuimden vanwege ziekhuisbezoeken, welke gemiddeld 10 uur betroffen. Vrouwen die meer uren per week werkten hadden meer IVF gerelateerd werkverzuim. Hoog opgeleide vrouwen hadden minder IVF gerelateerd verzuim dan vrouwen met een gemiddeld opleidingsniveau.

Om de kosten van werkverzuim door IVF te verminderen zou de focus op preventie van fysieke en psychische klachten moeten liggen.

Hoofdstuk 10

Kostenanalyse van een IVF en ICSI behandeling

In dit hoofdstuk werden de kosten van een eerste IVF en een ICSI behandeling per behandelingsfase, per cyclus en per doorgaande zwangerschap beschreven. Ook de kosten van een behandeling met ingevroren "rest" embryo's (cryo's) werden berekend. De gegevens over de kosten zijn verkregen uit 4 IVF centra, 2 academische, 2 niet academische en één transport ziekenhuis. De behandelgegevens zijn verkregen via de IVF registraties van het nationale cohort onderzoek (zie hoofdstuk 2), via jaarverslagen van drie IVF centra en via de nationale infertiliteit registratie (LIR).

De gemiddelde kosten van een IVF en ICSI behandeling waren bijna € 2500. De totale kosten van de behandeling worden voor het merendeel bepaald door de kosten voor medicatie. Bij vrouwen vanaf 34 jaar stegen de gemiddelde kosten per doorgaande zwangerschap door hogere kosten voor medicatie (hogere gemiddelde doses per cyclus) en dalende kans op zwangerschap. De kosten van bewaring, ontdooiing en terugplaatsing van ingevroren embryo's waren gemiddeld € 550. De kosten van een ICSI behandeling waren 8% hoger dan voor IVF door hogere kosten van apparatuur en arbeidsintensievere laboratorium procedures. De totale kosten per doorgaande zwangerschap per ICSI behandeling lagen echter lager dan

bij IVF vanwege de hogere kans op succes bij ICSI. Gemiddeld waren de kosten van een IVF/ICSI behandeling € 10.250 per doorgaande zwangerschap.

Hoofdstuk 11

Doelmatigheid van een IVF of ICSI behandeling

Dit hoofdstuk beschrijft een kosteneffectiviteit analyse van een behandeling IVF gestart bij paren die voldeden aan de NVOG richtlijn IVF ("direct- IVF"), in vergelijking met paren waarbij de behandeling één jaar langer zou worden uitgesteld. De berekening werd uitgevoerd met behulp van twee predictie modellen. Eén model is ontstaan uit een onderzoek naar de kans op zwangerschap één jaar na de start van IVF of ICSI in Nederland (zie hoofdstuk 2). Het andere model ontstond uit de studie naar de kans op een spontane zwangerschap op de wachtlijst voor IVF of ICSI (zie hoofdstuk 4). De prognostische factoren in de modellen waren leeftijd van de vrouw, diagnostische categorie, de duur en de aard van de subfertiliteit. De kosten van een IVF/ICSI behandeling zijn verkregen uit een steekproef van paren die een eerste IVF en ICSI behandeling ondergingen (zie hoofdstuk 10). De kosten van een behandeling IVF en de daaruit voortvloeiende kosten van een bevalling en de neonatale zorg werden vergeleken met de kosten indien de zwangerschap spontaan zou zijn ontstaan. Hierbij werd ook rekening gehouden met de grotere kans op een meerling met IVF/ICSI.

De kosteneffectiviteit ratio is het verschil in kosten per levend geborene bij direct een behandeling IVF/ICSI in vergelijking tot de kosten bij één jaar uitstel van IVF, gedeeld door het verschil in kans op een levend geborene tussen de twee scenario's. De kosteneffectiviteit ratio's lagen tussen de € 10.000 en € 50.000 per levend geborene. Voor vrouwen met endometriose was de kosteneffectiviteit ratio net onder de € 10.000 vanaf 34 jaar. Voor alle andere diagnostische categorieën, ongeacht de leeftijd ligt de kosteneffectiviteit ratio hoger. Voor vrouwen met een onbegrepen subfertiliteit ligt de ratio op € 30.000 vanaf 32 jaar en 3 jaar subfertiliteit.

Uitstel van IVF bespaart kosten tegen een kleine vermindering van het totaal aantal zwangerschappen. De kosteneffectiviteit van IVF wordt bepaald door de diagnostische categorie, de leeftijd van de vrouw en de duur van de fertiliteitstoornis, maar ook van de maatschappelijke bereidheid om te betalen voor de kosten van een extra levend geborene.

Hoofdstuk 12

Algemene discussie

In dit hoofdstuk worden de antwoorden op de onderzoeksvragen en de belangrijkste conclusies en aanbevelingen gegeven:

1. In Nederland was de kans op een doorgaande zwangerschap gemiddeld 24% na een eerste cyclus IVF/ICSI. Één jaar na de start van de behandeling was de kans 45%.

De zwangerschapskans met IVF/ICSI was voornamelijk afhankelijk van de leeftijd van de vrouw, voor een deel van de duur van de subfertiliteit en een eventuele eerdere zwangerschap en niet van de diagnostische IVF categorie. Het predictie model voor de kans op zwangerschap met IVF/ICSI zou gevalideerd moeten worden met gegevens van een nationale uniforme registratie van fertiliteitsbehandelingen en zou ook levensstijl factoren moeten bevatten.

2. Per IVF centrum verschilden de kansen op een doorgaande zwangerschap, één jaar na de start, tussen de 36% en 55%. Voor een klein deel worden de verschillen verklaard door de verschillen in patiënten populaties. Er zouden meer klinische en niet-klinische voorspellende variabelen geregistreerd moeten worden om meer duidelijkheid te krijgen over de verschillen tussen de IVF centra.

3. De gemiddelde kans op een spontane zwangerschap indien een IVF/ICSI behandeling met één jaar zou worden uitgesteld was 9%. Binnen één jaar na stoppen met IVF, was de kans op een spontane zwangerschap gemiddeld 7%. De kans op een spontane zwangerschap is zowel vóór als ná stoppen met een IVF behandeling, afhankelijk van de leeftijd van de vrouw, of ze ooit eerder zwanger is geweest, de oorzaak en de duur van de subfertiliteit. De counseling van paren op hun kans op een spontane zwangerschap zou gebaseerd moeten zijn op predictie modellen, waarin levenstijl factoren moeten worden meegenomen.

4. Rokende vrouwen en vrouwen met overgewicht (BMI ≥ 27 kg/m^2) hadden 30% minder kans op een zwangerschap met IVF. Eveneens werd de kans op een spontane zwangerschap na stoppen met IVF verlaagd door roken, overgewicht, cafeïne en alcohol. Een grote prospectieve studie naar de invloed van levenstijl factoren tijdens fertiliteits-behandelingen zou nog uitgevoerd moeten worden.

5. Angst en depressie vóór en tijdens een IVF behandeling, verkleinden niet de kans op een IVF zwangerschap en had eveneens geen invloed op de kans op een voortijdig afgebroken behandeling. "SCREENIVF", afgenomen voorafgaand aan een eerste IVF behandeling gaf in 75% van de vrouwen juist aan of zij wel of niet risico liepen op psychische problemen na een behandeling. De sensitiviteit van de test zou nog verbeterd kunnen worden. Bij onderzoek naar de invloed van negatieve emoties en fertiliteit zou onderzoek naar samenhang met levensstijl factoren niet mogen ontbreken.

6. De gemiddelde kosten van een IVF/ICSI behandeling waren € 10.250 per doorgaande zwangerschap.

De kosten van werkverzuim door IVF, waren € 600 per eerste cyclus. Door lichamelijke en psychische klachten te voorkomen, zouden de kosten van het werkverzuim door IVF aanzienlijk verminderd kunnen worden.

Voor vrouwen uit alle diagnostische categorieën boven de 32 jaar lagen de kosteneffectiviteit ratio's voor direct IVF in vergelijking met uitstel van IVF met 1 jaar, in een range tussen de € 10.000 en € 25.000 per levend geborene. Behalve voor vrouwen met een onbegrepen subfertiliteit. Om in dezelfde range te vallen zouden zij bovenop de drie jaar die de huidige richtlijn aangeeft, de IVF behandeling minstens nog één jaar langer moeten uitstellen.

Dankwoord

De eerste documenten over een op handen zijnd onderzoek naar de effectiviteit van de richtlijn IVF die ik gevonden heb dateren uit 1996. Dat was ver voordat ik erbij betrokken raakte. Mede dankzij de inspanningen van Didi Braat werd de subsidie voor het wachtlijst onderzoek naar de kosteneffectiviteit van IVF binnengehaald. Bij de start van het onderzoek ging het voor mij nog slechts om het verzamelen van de landelijke registraties van IVF behandelingen, zonder het uiteindelijke doel om te promoveren. De samenwerking en betrokkenheid van zoveel mensen hebben echter de morele druk hoog genoeg opgevoerd om het promotietraject voort te zetten.
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Curriculum Vitae

Bea Lintsen werd op 19 november 1963 als vijfde en laatste kind in het gezin geboren. Ze doorliep in haar geboortedorp Lent de R.K. meisjes school en behaalde haar VWO diploma aan het Canisius College te Nijmegen.

Na de middelbare school bepaalde letterlijk het lot dat ze één jaar als uitwisselingsstudent naar de Verenigde Staten ging. Ze lootte namelijk niet alleen uit voor de studie geneeskunde, maar ook voor 4 parkeerstudies in de paramedische sector. In 1983 startte ze de studie geneeskunde in Nijmegen. Na het behalen van haar doctoraal examen is zij in de wachttijd voor haar co-schappen student assistent geweest op de afdeling Pathologie.

Ze studeerde af in 1991, begon als invallend "huisarts" te Oss en was wisselassistent in het ziekenhuis de Gelderse Vallei te Ede voor verschillende specialismen. De slechte arbeidsmarkt en het avontuur dreef haar en haar partner Jos voor één seizoen naar het eiland Mallorca om daar als arts voor toeristen te werken.

Terug in Nederland begon zij als bedrijfsarts, maar keerde snel ze terug naar de kliniek. Haar carrière in de fertiliteit startte ze als fertiliteitarts in het Sophia ziekenhuis te Zwolle. In 1997 maakte ze de overstap naar Nijmegen alwaar ze tot op heden werkzaam is als IVF-arts aan het Universitair Medisch Centrum St Radboud op de afdeling Voortplantingsgeneeskunde.

Ze startte het onderzoek dat heeft geleid tot dit proefschrift naast haar huidige werk in 2002.

Sinds 1994 is zij getrouwd met Jos Dresen, datzelfde jaar werd hun dochter Juul geboren en in 1996 hun dochter Noortje. Wielrennen, ATB-en, paardrijden en hardlopen zijn haar hobby's.