Stress and IVF

clinical consequences

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Aan mijn ouders

Contents

1

General introduction

Demographic changes in the 20th century have led to a drastic rise of the mean age at which women deliver their first child. This can be attributed to higher educational levels and increased participation of women in the working process, alongside with the introduction of reliable and easy available contraceptive methods. The overall incidence of infertility has remained relatively unchanged over the past three decades.

What did change was the evaluation and the treatment of sub-fertile couples. The introduction of several assisted reproductive techniques (ART), for example In vitro fertilisation treatment (IVF), have led to an improved prognosis and as a result a structured diagnostic work-up. Furthermore, the more individualistic society together with the greater media attention for health matters in general and fertility issues in particular, have led to an increased demand for advice, evaluation and treatment.
Nowadays, approximately ten percent of Dutch couples (van Balen et al. 1997) suffer from a fertility disorder and about half of them are treated with IVF or intracytoplasmic sperm injection (ICSI). As a consequence, one out of every 55 children born in the Netherlands is conceived through IVF (Kremer et al. 2002).

In the Radboud University Medical Centre more than 1000 IVF cycles are started. The medical procedure is more or less standard. A long IVF protocol is currently used. Pituitary down-regulation is achieved through a GNRH analogue (Decapeptyl®, Ferrring, Hoofddorp, the Netherlands). Ovarian hyper-stimulation is realized with recombinant follicle stimulating hormone (Puregon®, Organon, Oss, The Netherlands).Thirty-six hours after the injection with human chorionic gonadotropin (Pregnyl®, Organon, Oss, The Netherlands) trans-vaginal oocyte pick-up (OPU) is performed. The morning after injection or insemination the fertilisation of the oocytes is evaluated. Three days after OPU one or two of the best quality embryos are transferred. The luteal phase is supported by intravaginal progesterone for fifteen days after OPU (Progestan®, Organon, Oss, the Netherlands).

I Prediction

Over the years several models have been published to predict the chance of pregnancy both spontaneously (Eimers et al. 1994) and after IVF (Templeton et al. 1996). The models consist of factors that were found to be related to pregnancy; age, duration of infertility, and type of infertility. Unfortunately, these models tend to be population specific and should therefore be tested in another population before being implemented elsewhere. In IVF age was at first found to be the best predictor of treatment outcome (Templeton et al.1996). On the other hand, the variability in ovarian ageing in the general population suggests that chronological age is a relatively poor indicator of the ovarian age in the individual. Furthermore, the costs, logistics and risks involved with IVF and the importance of accurate prognostication, have stimulated efforts to find other more accurate factors. Given the fact that fertility was shown to decline over the age of 30 (Schwartz et al. 1982) and an increased decline in women in women over 35 years of age (van Noord-Zaadstra et al. 1991), it was logical to look for markers related to this assumed decline in ovarian reserve (te Velde et al. 2002).

It is important to note that becoming pregnant is a complex multifactorial process and the size of the follicle cohort is more closely related to ovarian response than to the chance of pregnancy. Age was found to be related to a decline in both quality (Volarcik 1998) and quantity (Faddy 1992) of the ovarian pool. The declining oocyte quantity is associated with menopausal transition and menopause. The quality of the ovarian pool is related to pregnancy and fertility. The deterioration over time is attributed to accumulation of damage, such as oxidative stress (Tarin 1995). The fact that lower pregnancy rates (both after IVF and spontaneously) were found in women after exhibiting a poor response in IVF implies a direct relation between quality and quantity of the follicle pool (Lawson et al. 2003). On the other hand younger poor responders have shown reasonable pregnancy rates (Hanoch et al. 1998). The relation between the quantity and the quality of the ovarian pool therefore needs further exploration.

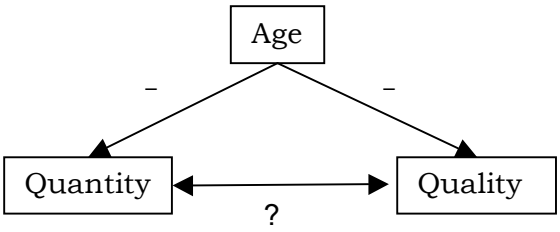

Figure 1: relation between age and quantity and quality of the ovarian pool (according to: van Rooij, thesis 2003)

Hormonal measurements in the early follicular phase were found to be associated with ovarian reserve. Ovarian reserve is defined as the number of primordial follicles. FSH is believed to indirectly reflect the size of the antral follicle cohort. Elevated concentrations of FSH in blood were found to be associated with poor ovarian response in IVF (Muasher et al. 1998). Since the growth of antral follicles is totally dependent on FSH, it was hypothesized that FSH-isoforms could provide additional information. Inhibin B levels decline before FSH levels rise, therefore low Inhibin B concentration in blood was suggested to be an even earlier marker of diminished ovarian reserve (Seifer et al. 1997). Basal ultrasound measurements of antral follicle count (Chang et al. 1998) and ovarian volume (Syrop et al. 1999) were introduced as direct morphological markers of ovarian reserve. Anti-Mullerian hormone is solely produced by granulosa cells (Baarends et al. 1995, Rajpert-De Meyts et al. 1999) and it reflects the pool of (pre)antral follicles. It was therefore introduced as a marker of ovarian reserve by van Rooij et al. (2002).
The clomiphene citrate challenge test is a dynamic stimulation test and considered to be an even more sensitive test. In a subgroup of our population no predictive capacity of this test was found (unpublished data), as a result we did not include this test in additional research.

In part one of this thesis pre-treatment factors, currently being presented as reliable and useful tools in the work-up of infertile women were evaluated and a new marker, FSH-isoforms, was tested.

II Stress

The hypothesis of the relationship between fertility aspects and psychological issues has come a long way. There is controversy whether psychological distress causes or results from infertility (Stanton et al. 2002). In former days, psychogenic infertility was practically used as a synonym for medically unexplained infertility (Batstra et al. 2002). However, advancements in diagnostic, therapeutic and scientific methodology in infertility matters can no longer sustain this simplistic view (Wischmann 2003).

Infertility is a chronic stressor that frequently endures for several years (Domar et al. 1993) and can be characterised as threat, uncertainty, uncontrollability and loss. These aspects may easily evoke anxiety (Stanton & Dunkel-Schetter 1991) and uncontrollability may result in depressive feelings (Seligman 1975).

The number of couples taking advantage of IVF has increased considerably in the last decade. The success rate did not show the same increase and is currently just over 50% cumulatively after three attempts. This implies that increasing numbers of couples will be faced with unsuccessful treatment, leaving few or no treatment alternatives. The IVF treatment is associated with far greater anxiety than other fertility treatments, due to the last chance notion. (Dennerstein & Morse 1988, Litt et al. 1992). The stress of infertility is further reflected by the fact that half of all women experience fertility problems as being the worst event that has ever happened to them (Mahlstedt et al. 1985) and infertility was defined as a disease by the World Health Organisation. A special meeting on this topic, dealing with the medical, psychological, ethical and social aspects was organised by the WHO in 2001 (www.who.int/reproductive-health/infertility).

Not only psychological responses to infertility and assisted reproductive technologies (ART), but also psychological issues related to treatment outcome in ART are the subject of numerous studies. Furthermore, coping strategies and stress management interventions in ART were developed and studied to improve the well-being of the patient.

Outcome

In the 'Guidelines for Counselling in Infertility' by the ESHRE it was stated that 'unexplained infertility is not in most cases equivalent to psychogenic infertility' (Boivin 2002). On the other hand, evidence is mounting that stress may alter biomedical processes relevant to reproduction and therefore exert an effect. In most

studies stress was examined with standardized questionnaires often on anxiety and depression before or during treatment, and where successful outcome of treatment was defined by pregnancy. Higher levels of anxiety or depression were associated with lower pregnancy rates (Demyttenaere et al. 1998, Domar et al. 1999, Kee et al. 2000, Klonoff-Cohen et al. 2001, Sanders & Bruce 1999). Others could not find this association (Ardenti et al. 1999, Csemiczky et al. 2000, Harlow et al. 1996, Slade et al. 1997).

Almost all studies were performed in a (clinical) treatment setting, mostly related to in vitro fertilization treatment. Unfortunately, only the minority of the studies have a more or less systematic approach. However, taking all available studies into account the picture emerges that stress could well be a co-factor in the outcome of treatment.

Drop-out

Relative high percentages of patients' drop-out in IVF-treatment were reported for other reasons than running out of funds or physicians telling them to discontinue, for instance psychological factors (Land et al. 1997). Additionally during treatment the psychological burden of treatment was found to be a major factor in patient drop-out (Olivius et al. 2004). Several authors reported drop-out rates up to 65% that were related to psychological factors (Hammarberg 2001, Olivius 2002, Osmanagaoglu 1999, Schroeder 2004).

Mechanisms

First a distinction has to be made between direct and indirect effects of stress. The direct effects refer to the autonomic nervous system, the (neuro) endocrine and the immune system. The indirect effects imply health changes affecting fertility resulting from changes in health behaviour (Vingerhoets & Perski 2000).

The relationship between psychosocial stressors and the effects on the sympathetic medullar system and the hypothalamic-pituitary-adrenal (HPA) axis was subject of numerous studies throughout the years. However, studies linking the sympathetic system and the HPA axis with (in)fertility are scarce (e.g. Sanders & Bruce 1997). Thus, the relationship between stress, the release of hormones and the effects on fertility remain obscure and as a result only few psychobiological mechanisms were published.

Direct effects

Stress could interfere with fertility via inhibition of the GnRH pulse generator in the hypothalamus (Ferin et al. 1999). Catecholamines may affect uterine blood flow (Schenker et al. 1992), and/or steroid genesis by granulosa cells and oocyte quality (Michael and Cooke 1992). Higher serum cortisol/follicular cortisol ratio was associated with higher pregnancy rates (Lewicka et al. 2003), whereas subfertile women were found to have elevated levels of cortisol compared to fertile controls (Csemiczky et al. 2000). Furthermore, stress was found to be associated with activated T-cells and reduced implantation (Gallinelli et al. 2001). In conclusion: several hypotheses concerning the direct effects of stress on fertility were presented throughout the years, but no clear picture emerges.

Indirect effects

Changes in health behaviour due to stress, i.e. smoking, alcohol intake, or weight gain may also affect fertility and treatment success. Since the indirect effects were not an integral part of this thesis, only a synopsis of the most relevant literature is presented.

The strongest evidence for a negative impact on fertility was found for smoking. All aspects of fertility were found to be affected, including number and quality of oocytes, percentage of fertilization, implantation, pregnancy and miscarriage (Crha et al. 2001, El-Nemr et al. 1998, Lintsen et al. 2005, Paszkowski et al. 2002). Alcohol consumption was found to be predictive of infertility in women over 30 years in a large cohort study (Tolstrup et al. 2003). Both female and male alcohol consumption were found to have negative impact on the outcome of IVF (Klonoff-Cohen et al. 2005). Obesity was found to interfere with fertility (Pasquali et al. 2003, Pettigrew et al. 1997). Furthermore reduced success rates during IVF treatment were found in obese women (Fedorcsak et al. 2004, Lintsen et al. 2005, Munz et al. 2005, Spandorfer et al. 2004).

Intervention

Systematic evaluation of intervention in infertility counselling, so with a control group and follow-up, was only performed in 25 out of 380 studies (7%). In general it was concluded that pregnancy rates were unlikely to be affected by psychosocial interventions. Relaxation techniques and interventions based on a behavioural medicine approach were found to increase pregnancy rates after ART treatment.

The evidence however being scarce, since only few controlled studies exist. Psychosocial interventions were more effective in reducing negative affect than in changing interpersonal functioning. Group interventions that had emphasized education and skills training were found to be significantly more effective in producing positive change across a range of outcomes than counselling interventions which emphasised emotional expression and support and/or discussion about thoughts and feelings related to infertility (Boivin et al. 2003).

In part two of the present thesis psychological and biomedical factors were integrated and the relation with the outcome of IVF was studied. (see figure 2)

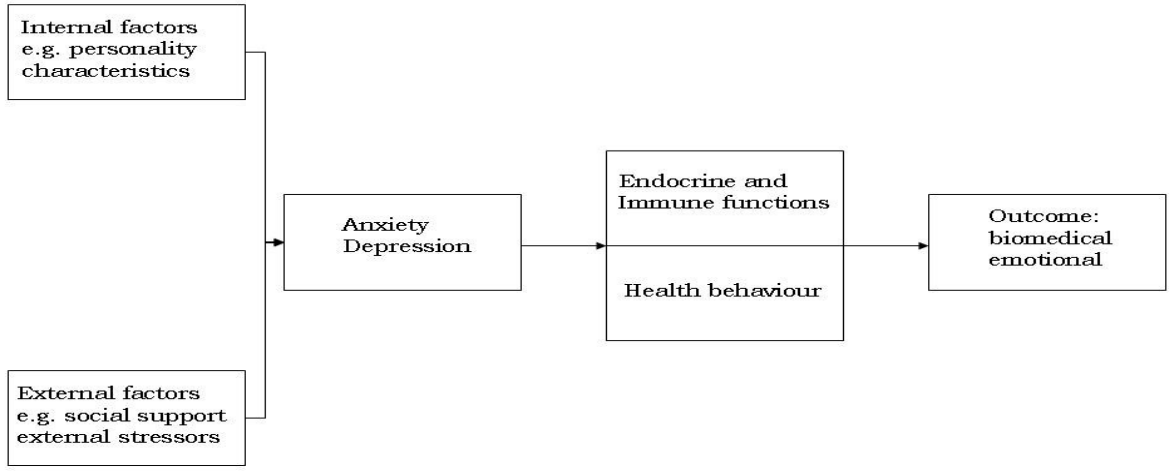

Figure 2: Biopsychosocial model of fertility
(according to: Verhaak, thesis 2003)

III Treatment

IVF being the most invasive and intensive form of infertility treatment can obviously lead to distress. Patients even indicated that treatment is more of a psychological than a physical stressor since the outcome is unpredictable (Eugster et al. 1999).
Previously a thesis on the 'emotional impact of unsuccessful fertility treatment in women' was published on the same cohort of women (Verhaak 2003).
Factors that contribute to the emotional response to a severe stressor include personality characteristics (Clark 1994), biases in information processing (Williams 1996), stressor-related cognitions (Beck & Clark 1997), coping (Lazarus & Folkman 1984) and social support (Cohen & Wills, 1985). Based upon a stress vulnerability model a hypothetical course of women's anxiety and depression in the event of unsuccessful treatment was launched. It was found that women with a passive coping style and cognitions of helplessness regarding fertility problems seem to be most vulnerable for developing severe emotional problems as the result of unsuccessful treatment.

The assessment points of the present thesis are being indicated in figure 3.

Before treatment (T1)

In general, it may be concluded that at the start of the treatment, IVF patients with respect to depression levels did not differ from norm groups (Fekkes et al. 2003, Verhaak et al. 2001), while the results on levels of state anxiety were unequivocal: some studies showed higher levels (Salvatore et al. 2001, Slade et al. 1997), others showed no difference with the norm groups (Edelmann et al. 1994, Verhaak et al. 2001).

During one treatment cycle (T2)

Several studies focussed on the emotional response during treatment. In general an increase in distress during the course of treatment was found and the oocyte-pick up and the pregnancy test were found to be the most stressful moments of the IVF cycle (Klonoff-Cohen 2001, Yong et al. 2000).

After one or more treatment cycles (T3)

The most consistent finding in the literature was an increase in depression after one or more unsuccessful treatment cycles (Hynes et al. 1992, Lok et al. 2002), the picture regarding anxiety is equivocal (Slade et al. 1997, Visser et al. 1994). The observed stress response to failed treatment consists of a complex interplay of the acute burden of (failed) treatment and the chronic nature of the threatening definitive infertility (Verhaak et al. 2001).

Follow-up (T4)

Long term studies are lacking, but cross sectional studies showed less positive affect in women several years after (un)successful IVF (Hammarberg et al. 2001, Freeman et al. 1987). Longitudinal studies would make it possible to investigate the course of anxiety and depression, not only at several months post treatment, but also at long term follow-up.

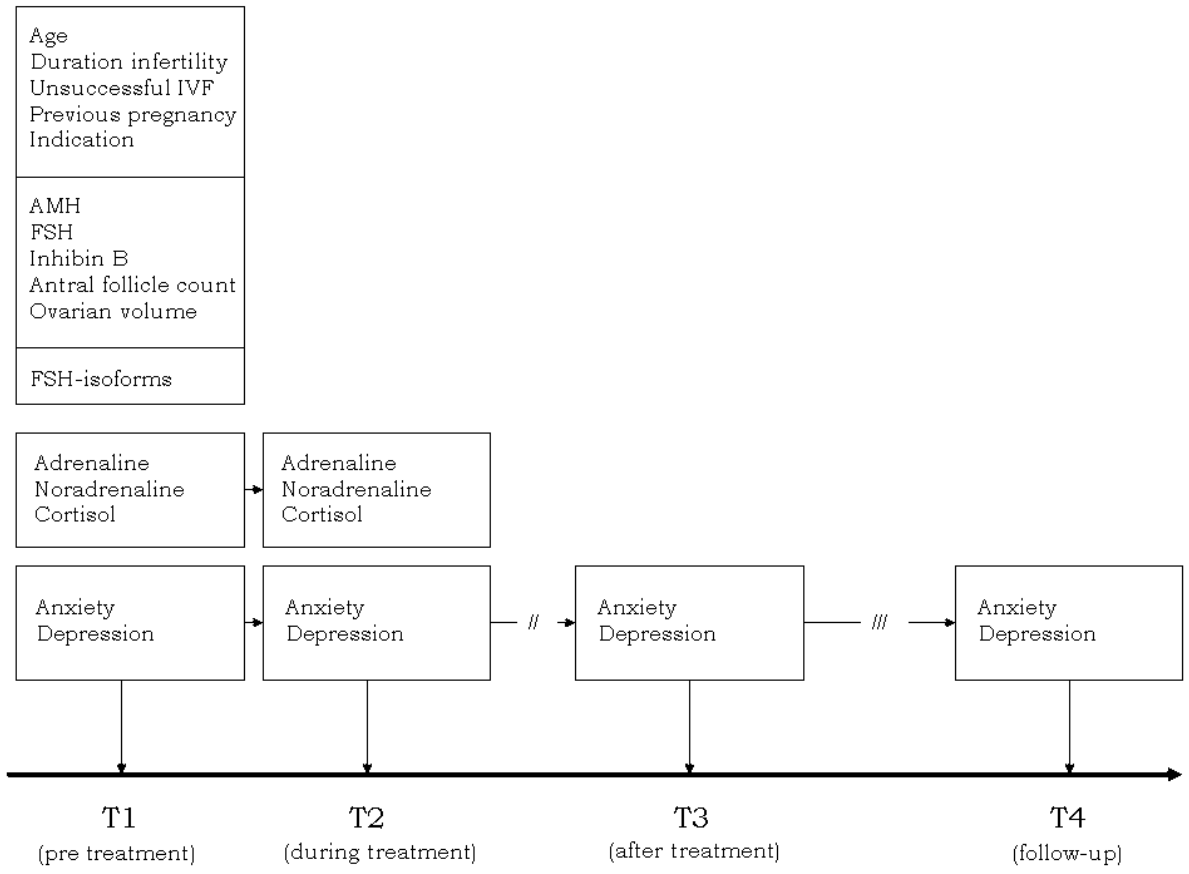

Figure 3: Study schedule

In part three of the study the pscychological consequences of IVF treatment were studied 6 months and at least 3 years after the last treatment cycle.

Study design & objectives

The present study consisted of a retrospective part, in which data were used from the Radboud University Medical Centre from 1991 up to 1999 to validate an existing model. In the prospective part patients were included between 1999 and 2000. In total 380 patients were eligible and willing to participate. In 2003 the study was completed with a follow-up study of the cohort. Different selections of patients were used in different chapters.

Next to the integration of biomedical and psychological factors and the mechanisms involved, the present thesis enabled us to do a follow-up on the implications and consequences of unsuccessful IVF treatment. An issue that receives a considerable amount of attention through clinical, descriptive and empirical studies.
An overview of existing empirical research on emotional adjustment to IVF over the last 25 years was presented by Verhaak et al. (2006). Being informed about the long-term follow-up of women after definitively failed treatmen could indicate the need for additional research focussing on tailored interventions after treatment.

The aim of this thesis was to study IVF by integrating gynaecological and psychological issues. Existing prognostic biomedical factors and models were chosen as the starting point. Since IVF is one of the more 'controlled' medical regimes, it was analysed whether these biomedical factors could explain the variance in treatment outcome. The first step was therefore to validate an existing model and other prognostic factors in a clinical setting. The next step was to integrate psychological factors and to biomedical factors in a prospective longitudinal cohort design to study additional explained variance in the outcome. Furthermore, the stress hormones were measured to study an explanatory mechanism. Lastly the consequences of IVF on the psychological outcome were studied in a prospective follow-up manner since the outcome of the process is more than that of cumulative pregnancy rates. Consequently, implications and recommendations for future treatment and future research are being discussed.

The thesis consists of three parts;

I Study existing and new prognostic biomedical factors in IVF treatment

II Study the integrated model of psychological and biomedical factors and the mechanisms involved on the course and outcome of IVF

III Study the consequences of IVF on the psychological outcome and discuss recommendations for the future

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Part I

Prognostic biomedical factors in IVF

2

External validation of the 'Templeton model' for predicting success after in-vitro fertilization

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Abstract

This study aimed at externally validate the prognostic model presented by Templeton (1996) for a live birth resulting from IVF treatment. Data were used from the University Hospital, Nijmegen, the Netherlands, from March 1991 to January 1999. The predictive capacity of the model in our population discriminated between a group of women that had a low probability of success and that had a relatively high probability. Despite these encouraging findings, our data show that implementation of the model in clinical decision making remains difficult. The 'Templeton' model is not applicable nor usable in daily clinical practice, because the model did not give more information about the prognosis for the vast majority of the patients. The search for better prognostic factors resulting in better predictive models should therefore continue.

Introduction

Modern medicine is more and more concerned with making choices from seemingly unlimited options. As a part of the decision making, for each individual, the physical, the psychological, as well as the financial costs should be weighed against the probability of success. Although it is practically impossible to predict the individual chance of a live birth in a couple accurately, prognostic models can help to encounter these matters in a rather objective way. They can also act as a convincing tool in individual counseling for both patients as well as physicians. It remains, however, to be seen how many patients refrain from treatment if their prognosticated chance is poor.

In the field of infertility several authors have launched their models for the probability of pregnancy. Before any of these models can be implemented in clinical practice good external validation is required (Stolwijk et al. 1998). The predictive accuracy of a prognostic model can be expressed by calibration and discrimination (Harrel et al. 1996). Calibration refers to the amount of bias in the predictions, while discrimination refers to the ability to separate patients with different outcomes. Unfortunately, prognostic models after IVF for the probability of pregnancy presented in the literature have often not been validated (Haan et al. 1991; Hughes et al. 1989; Templeton et al. 1996). Stolwijk et al. (1996) presented a prognostic model which was externally validated; these tests in another centre proved that these models could not predict well. Templeton et al. (1996) developed a model to predict pregnancy after treatment with in-vitro fertilization (IVF) by using data of 26,389 women treated in all IVF centres in the UK. Although a model based on such a large population seems rather confirmative, it might not predict well in other populations. To examine the external validation, a model should be applied to other data than those which the model was based upon. To our knowledge this external validation of the 'Templeton model' has not been done before. Therefore we started a retrospective study to validate the model and thereby estimate its clinical usability.

Materials and Methods

Data were used from couples who underwent their first IVF treatment after March 1991 in the University Hospital Nijmegen, the Netherlands. All cycles, performed up to January 1999, were included. In concordance with the cycles included in the

study of Templeton et al. cycles were excluded in which intracytoplasmic sperm injection was performed or in which donor gametes or frozen embryos were used.

All cycles in which hormonal stimulation was initiated were included, regardless whether follicle aspiration or embryo transfer was performed. Ovarian stimulation was most often performed by means of a long protocol of gonadotrophin-releasing hormone agonist, that was started on day 21 of the previous cycle, followed by human menopausal gonadotrophin (HMG). In general three embryos were transferred, but since January 1997 a maximum of two were transferred.
The predicted probability of achieving a live birth after IVF (P) was calculated by means of the model presented by Templeton et al.: $P = 100 \times \exp(y) / [1 + \exp(y)]$.
Where y was defined as $y = -2.028 + [0.00551 \times (age - 16)^2] - [0.00028 \times (age - 16)^3] + [i - (0.0690 \times$ no. of unsuccessfull IVF attempts)] - (0.0711 × tubal subfertility) + (0.7587 × live birth after IVF) + (0.2986 × previous pregnancy after IVF which resulted not in a live birth) + (0.2277 × live birth which was not a result of IVF) + (0.1117 × previous pregnancy, not after IVF and which did not result in a live birth). Tubal subfertility and previous pregnancies were dichotomised in the model; 1 if applicable, 0 if not. The indicator 'i' was a value used to represent the infertility duration in years and was 0.2163 if the infertility duration was between 1 and 3 years, -0.0839 if between 4 and 6 years, -0.1036 if between 7 and 12 years, and -0.4179 if 13 years or more.

Templeton`s model is based upon information from clinic forms which do not specify criteria for diagnosis, as pointed out by Craft & Forman (1997). The variable 'diagnosis', as used in the model, is therefore the result of different work-ups and criteria. Furthermore, other variables were not specified at all. Because of these, we made a few assumptions to define the following variables in the model;
1. Age: age of the woman at the specific IVF cycle.
2. Duration of infertility: duration of subfertility at the first IVF cycle.
3. Unsuccessful IVF attempts: the total number of previous IVF cycles in which no ongoing pregnancy was achieved.
4. Previous pregnancy not resulting in a live birth: spontaneous abortion or an ectopic pregnancy.
5. Tubal pathology: tubal pathology exclusively.
Furthermore, because of limitations in the data available, we defined:

6. The predicted outcome: live birth. Because of incomplete follow up we assumed for our calculations that all ongoing pregnancies, which are pregnancies that continued for at least 12 weeks after embryo transfer, resulted in live births.
We performed 3 external validations in which we intended to study the influence of different definitions by comparing the outcome of these 3 validations:
A. Following the assumptions mentioned above.
B. Woman's age at the first IVF cycle (instead of at the specific IVF cycle).
C. Tubal pathology exclusively or in combination with one or more other subfertility diagnoses (male factor, endometriosis, or cervical factor) (instead of tubal pathology exclusively).

We evaluated the predictive performance of the model by means of (I) the c index, which indicates the overall discriminative performance (Harrell et al. 1982, 1996), and (II) compared observed and predicted proportions of success for groups with a low probability (below 5%, below 10%) and a high probability (20% or higher). We presented predicted proportions with mid-p exact 95% confidence intervals(CI) (Vollset, 1993). The c index (number of concordant pairs + 0.5 × the number of tied pairs/total number of pairs) can be interpreted as the probability of a correct prediction for a random pair that comprises a woman with an ongoing pregnancy and a woman without an ongoing pregnancy. A c index of 0.5 indicates that the predictions made for the whole population are bad; such a prediction is comparable to a flip of a coin. A c index of 1 indicates the ability to make perfect predictions.

Results

In total the data of 1292 couples who started a first IVF treatment since March 1991 in the University Hospital Nijmegen, the Netherlands, were used. Up to January 1999 they underwent 2756 IVF cycles. Of 35 couples who underwent 75 cycles, the duration of infertility was unknown; of two of them the subfertility diagnosis was also unknown. Of another 3 couples, who underwent 5 cycles, it was unknown whether tubal pathology was present. Of one couple who underwent two cycles it was unknown whether any non-IVF live births were present. After excluding data of these couples, we could use the data of 1253 couples who underwent 2674 IVF cycles for the external validation of the model of Templeton et al.

The mean age of the women at the beginning of treatment was 32.8 years(SD=4.0; range 22-44; median 33 years) and the mean duration of infertility was 3.7 years (SD=2.5; range 1-21; median 3 years). The mean number of previous unsuccessfull IVF attempts was 0.8 (SD=1.0; range 0-6; median 0 unsuccessfull attempts).
In the validation 7% of the cycles were preceded by at least one previous live birth after IVF, 6 % by at least one previous IVF pregnancy not resulting in a live birth, 13 % by at least one live birth (excluding IVF births) and 22 % by at least one pregnancy not resulting in a live birth (excluding IVF pregnancies). From all cycles that were used in the validation, 47% were first cycles, 29% were second cycles, 16% were third cycles, 5% were fourth cycles and 2% were of a higher rank (range 5-8). The distribution of indications for treatment, also important to test Templeton's model, is depicted in Table I.

Table I: Indication characteristics of the couples at the start of the first IVF cycle (n=1253).

Indication for treatment	Frequency (%)
Tubal pathology exclusively	295 (23.5)
Male factor exclusively	300 (23.9)
Tubal pathology and male factor	60 (4.8)
Other reasons*	338 (27.0)
Idiopathic	260 (20.8)

*Other reasons include hormonal, endometriosis, cervical factor, or a combination with tubal pathology or male factor

In the first validation (A) in which we used the assumptions mentioned above, we found a c index of 0.629. In the second validation (B), where another way of defining the woman`s age was investigated, the c index was 0.632. In the third validation (C), where we looked upon the effect of another way to define the diagnosis, we found a c index of 0.628. Using the assumptions of validation A, we calculated the predicted proportions.

In Table II we present for each group of patients within a specific range of predictions (e.g. 0-<5%) the observed proportion of ongoing pregnancies with the 95% confidence interval. The observed proportions increase from 0.0% in the group

with a predicted probability of 0-<5% to 37.0% in the group with a predicted probability of ≥30%.

Table II: Predicted and observed probability of an ongoing pregnancy during an IVF treatment cycle (P) in the first validation.

	Predicted probability (%)						
	0-<5	5-<10	10-<15	15-<20	20-<30	≥30	Total
Observed							
Number of cycles	50	370	1116	924	187	27	2674
Number of ongoing pregnancies	0	34	179	180	67	10	470
Percentage P (95% CI)	0.0 (0.0-5.8)	9.1 (6.5-12.5)	16.0 (14.0-18.3)	19.5 (17.0-22.1)	35.8 (29.2-42.9)	37.0 (20.6-56.2)	17.6 (16.2-19.1)

In our population, the women with a low predicted chance (<10%) are relatively old (34-45 years) and never had a live birth after IVF treatment. Of these, the younger ones (34-36 years) all had a history of infertility of 4 years or more. The women in our population with a fairly high predicted chance (≥20%) generally were younger (66% was younger than 34 years) and most of them (86%) had a history of infertility of 1-3 years. The group with a high predicted chance (≥30 %) is characterised by women who all had a previous live birth after IVF.

Discussion

The comparison of the predicted and observed chances of success (Table II) shows that the model seems to be able to identify the women with a low chance and the women who have a high chance of achieving a live birth. Our c indices of approximately 0.6, however, suggest a poor predictive performance of the 'Templeton model'. In general, about 13.9% of the IVF-cycles will be successful, according to Templeton. Without any information of a patient, this will be the prior probability of success. A prognostic model is useful if it changes this prior probability in an accurate way. In the population seventy-six percent had a (posterior) predicted probability of 10-<20%. Such a prediction does hardly change

their prior probability. Thus for the main proportion of patients the model of Templeton showed no use.

In the model the relative importance of the presented factors can be deducted from the parameter estimates resulting from the multiple logistic regression model.
The 'duration of infertility' as well as 'previous pregnancies' play an important role (in the latter the number of pregnancies is multiplied by the regression coefficient) , whereas the influence of the woman's age is not so obvious. Therefore we made a calculation of the relative effect of the woman's age. For this purpose we used the formula presented in the model: $0.00551 \times (age - 16)^2 - 0.00028 \times (age - 16)^3$.

Table III: Women's ages and the resulting regression coefficients (Rc).

Age	Rc	Age	Rc	Age	Rc
20	0.07024	28	0.30960	36	-0.03600
21	0.10275	29	0.31603	37	-0.16317
22	0.13788	30	0.31164	38	-0.31460
23	0.17395	31	0.29475	39	-0.49197
24	0.20928	32	0.26368	40	-0.69696
25	0.24219	33	0.21675	41	-0.93125
26	0.27100	34	0.15228	42	-1.19652
27	0.29403	35	0.06859	43	-1.49445

From Table III it becomes clear that 29 is the most favourable age to achieve a live birth after IVF, that the chance rapidly decreases when the patient becomes older and that the relative positive influence of low age decreases in younger women. Although the parameters used by Templeton et al. all contribute to the predictive capacity of the model, age still is a very important predictor. We could not find remarkable differences between the results of our original validation (A) and our second validation (B), suggesting that there is no significant influence of the definition of the woman's age. This was expressed by the virtually unchanged c index (from 0.629 to 0.632).
In our third validation (C) we compared the predictive value of tubal pathology in combination with other diagnoses as subfertility diagnosis with 'tubul pathology exclusively'. The c index hardly changed (from 0.629 to 0.628). Therefore we

concluded that the exact definition of 'tubal pathology' as subfertility diagnosis plays a minor role. This can be explained by the low regression-coefficient for 'tubal reasons for infertility' in the 'Templeton model' (-0.0711).
In our assumptions we chose to use ongoing pregnancy as our endpoint instead of live birth, because the follow-up of pregnancies was not accurately enough.
Data from our own clinic show that from July 1991 till December 1997 506 ongoing pregnancies resulted in 482 live births (95%). The predicted probabilities for a live birth will therefore underestimate the expected probabilities of ongoing pregnancy. We observed for the entire population that in 17.6% of the started cycles an ongoing pregnancy was achieved. The model by Templeton et al. predicted that in 14.4% (95% CI= 13.1-15.7%) of the started cycles a live birth would be achieved. Craft & Forman (1997) pointed out that Templeton reported an unexplained infertility incidence of over 30%, which they felt is very high, considering that patients were treated in tertiary fertility referral centres. Our data show a considerable lower percentage (20.8%) of unexplained infertility cases. Last but not least, the original study revealed big differences between the contributing centres, what could attribute to the poor reproducibility of the model.
The question raises whether the development of a better model is possible or not. Other promising predictive factors may increase the predictive value of a model, as pointed out by Craft and Forman (1997). For instance basal FSH (Sharif et al. 1998), or day 3 estradiol (Smotrich et al. 1995) showed better predictive value than age alone. Inhibin is regarded to be another promising predictor of the outcome of IVF (Lindheim et al. 1998; Seifer et al. 1997). Moreover, since new techniques and medication influence the results of assisted reproductive technologies, a prognostic model has a limited lifetime and needs constant adaption.

In conclusion: the model presented by Templeton et al. based upon an unrivalled large dataset, seems to be able to discriminate a group of women with a very low and those with a very high probability of achieving success after IVF in our population. However, for the majority of women the application of the Templeton model did not give any more certainty, because their prior and posterior probabilities hardly differed.

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3

Antimüllerian Hormone predicts ovarian responsiveness, but not embryo quality or pregnancy, after in vitro fertilization/intracytoplasmic sperm injection

Fertility and Sterility, in press

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Abstract

Antimüllerian hormone (AMH) and other markers of ovarian reserve were assessed to determine their predictive value with respect to treatment outcome. In a multivariate regression analysis AMH was found to be predictive of the number of oocytes and the number of embryos, but not of embryo quality or the chance of a pregnancy after IVF/ICSI.

Introduction

In IVF/ICSI treatment outcome is highly variable and difficult to predict. The reproductive function is related to age, but age is an inaccurate predictor of ovarian reserve. Indicators of ovarian reserve would candidate as predictors for the probability of an ongoing pregnancy after IVF/ICSI. With menopause being a rather clear endpoint of reproductive function, ovarian reserve is far more difficult to specify. It is often considered a clinical diagnosis: poor response, defined as a low number of follicles despite high dosages of gonadotrophins.

Since in counselling it would help both patients and doctors to be informed about the chances of a pregnancy, spontaneously or resulting from assisted reproductive technologies (ART), indicators of ovarian reserve have been sought and have been introduced in clinical practice. Basal hormonal tests measured in the early follicular phase; e.g. elevated FSH concentration in blood (Muasher et al. 1998), low Inhibin B concentration in blood (Seifer et al. 1997) have been suggested, but also basal ultrasonographical measurements, e.g. antral follicle count (AFC) (Chang et al. 1998), ovarian volume (OV) (Syrop et al. 1999), were found to be associated with ovarian reserve. However, for all these markers the predictive power appears to be low. Recently, a potentially new marker was put forward: antimüllerian hormone (AMH) (van Rooij et al. 2002).

Antimüllerian hormone is expressed after birth in the granulosa cells of healthy, small growing follicles (Baarends et al. 1995). It plays (in)direct roles in various phases of folliculogenesis, from the primordial to FSH-sensitive follicular stages (Durlinger et al. 2002, McGee et al. 2001). AMH serum levels were shown to correlate strongly with the number of antral follicles (Gruijters et al. 2003) and it has a relative stable expression during the menstrual cycle (Cook et al. 2000). Seifer et al. (2002) found a correlation between AMH serum levels and the number of oocytes retrieved during IVF treatment. AMH is by now presented as a good marker of the ovarian reserve (Visser and Themmen 2005).

To study the predictive value AMH conditional on other alleged predictors of treatment outcome, we included these different markers in a prospective study among couples treated with IVF/ICSI and correlated these with clinical outcomes, such as the number of follicles, number of embryos, embryo characteristics and probability of an ongoing pregnancy.

Materials and methods

Patients

Patients who started a new IVF/ICSI treatment at the Radboud University Nijmegen Medical Center, an academic tertiary referral centre in the east of the Netherlands were invited to participate in the study. Inclusion criteria were: age < 42 years, regular menstrual cycles, both ovaries present, no endocrine disorders. A long protocol with Decapeptyl® (Ferring, Hoofddorp, the Netherlands), Puregon® (Organon, Oss, the Netherlands) and Pregnyl® (Organon, Oss, the Netherlands) was used. Only first treatment cycles were included. A maximum of two embryos was transferred, three days after ovum pick up (OPU). Informed consent was obtained from 112 participants. This study was approved by the ethical committee of the institution. All participants were guaranteed confidentiality, and only the principal investigator (JS) had full access to the data.

Blood sampling and hormone measurements

On cycleday 3 before treatment, that is before the start of GnRH-analogue medication, women were monitored on predictiors of treatment outcome. Serum basal follicle stimulating hormone (FSH), Inhibin B and AMH were determined and ultrasound was performed measuring the antral follicle count and total ovarian volume.

Blood was collected by venapunction in dry tubes and serum was separated and frozen in aliquots at -20°C. Follicular Stimulating Hormone (FSH) in serum was determined by Fluorescence Immunoenzymometric Assay using a random access analyser (AxSYM, Abbott, Hoofddorp, the Netherlands). Serum inhibin B levels were measured using an ultrasensitive enzyme-linked immunosorbent assay (ELISA) (Serotec, Oxford, UK). Serum AMH levels were determined using an enzyme immunoassay kit (Immunotech, Marseille, France).

Ovarian ultrasound scanning was performed on the same day as the bloodsampling by one operator (J.S.) who was blinded to the results of the hormone assays. The sum of all follicles measuring 2-10 mm in mean diameter in both ovaries was established. Ovarian volume was calculated with the equation of an ellipsoid (0,526 x length x height x width) (Sharara and McClamrock 1999).

Outcome

Main outcome measure was a viable pregnancy. This was defined as a positive heartbeat on transvaginal ultrasound five weeks after embryotransfer (ET). Secondary outcome measures were: number of oocytes, number of embryos and quality of the embryos.

The embryo quality was dichotomized (good versus bad) based upon a composite score consisting of amount of fragmentation and the number of cells of the best 2 embryos (if applicable). Embryos with less than 20% fragmentation and 7 or more cells were defined as 'good' (Fisch et al. 2001).

Statistical analysis

Data analysis was performed by means of the SPSS-program (version 11.0 for windows, SPSS INC., Chicago, USA). For reasons of efficiency and costs, we compared all women who became pregnant (n=40) with an equal number (40 out of 72) of non-pregnant women.

For univariate comparison of the two independent samples we used the Mann-Whitney test, with respect to the non normal distribution of markers. The Spearman correlation coefficient was used to estimate the association between the different markers. A multivariate logistic regression analysis was used to find the best combination of independent predictors for clinical outcomes.

Results

One-hundred-and-twelve women were assessed on cycleday 3 prior to treatment. Forty (36%) achieved a viable pregnancy. These 40 patients were retrospectively compared with 40 randomly selected women out of the 72 remaining women without a pregnancy.

Table I: Population characteristics and markers of ovarian reserve

	Parameter values (range) N=80	Pregnant women (SD) N=40	Nonpregnant women (SD) N=40	p-value
Age (years)	27.6-41.9	34.1 (3.1)	34.9 (4.1)	.36
Body Mass Index (kg/m^2)	16.9-39.1	23.8 (3.3)	23.8 (4.3)	.95
Gonadotropins (IU)	800-5700	1854 (933)	2102 (942)	.24
Number of oocytes	1-30	10.7 (6.6)	10.1 (5.0)	.65
Number of embryos	1-22	6.7 (4.7)	6.3 (4.5)	.66
Embryo quality score	1-2	1.4 (0.5)	1.4 (0.5)	.65
FSH (IU/L)	1.8-14.4	6.6 (2.4)	7.0(1.9)	.50
Inhibin B (pg/mL)	5-161	87.3 (31.2)	95.8 (38.4)	.28
AMH (µg/L)	0.2-11.7	3.2 (2.6)	2.9 (2.4)	.49
Antral follicle count (n)	1-25	8.6 (4.2)	7.3 (3.6)	.14
Ovarian volume (cm^3)	1.6-24.8	6.3 (3.9)	6.0 (3.1)	.72

Table I shows patient characteristics and the ovarian reserve markers of pregnant and nonpregnant women. No statistically significant differences in any of these markers could be detected in univariate analysis.
AMH was found to be significantly correlated to the other predictors: FSH (r=-.42; p<.01), AFC (r=.52; p<.01), OV(r=.38; p<.01), but not with Inhibin B (r=.08; p=.47).

All these markers were included in a logistic regression analysis with pregnancy probability as primary outcome, thus including all 80 women in this study. The analysis did not reveal any meaningfull predictive capacity for any of the markers of ovarion reserve. In a similar logistic regression analysis, AMH proved to be predictive of the number of oocytes (t=2,5; p=.02) and the number of embryos (t=2.0; p=.05). The other reserve markers were not found to be significantly independently predictive of the number of oocytes or embryos. None of the factors showed predictive capacity with respect to the quality of embryos.

Discussion

In the present study serum AMH levels were found to be variable (range 0.2-11.7) and associated with ovarian responsiveness, but not with embryo quality and not with the probability to achieve a pregnancy. Other markers of ovarian reserve (biomedical, echoscopic and hormonal) were found to have an even poorer capacity to predict the number of oocytes, number of embryos, embryo quality or pregnancy after treatment.

The requirements for the ideal marker reflecting the decline in reproductive function are: biological plausibility, cross-sectional relation with age, mean longitudinal change and consistency of individual change (according to: van Rooij et al. 2005).
Basal FSH seemed to fulfill all criteria and was subject of many studies. However, in a review, Bancsi et al. (2003) concluded that basal FSH should not be regarded as a useful routine test for the prediction of IVF outcome. AMH was launched as a new marker of ovarian reserve by the same group (Van Rooij et al. 2002).

Fanchin et al. (2003) showed higher correlations for serum AMH levels and antral follicular count than for serum levels of inhibin B, FSH, estradiol and LH. We also found a high correlation between AMH and AFC, but the correlation-coefficient (0.52) was lower than previously reported i.e. 0.71 in 41 normal ovulatory women and 13 postmenopauzal women (De Vet et al. 2002) and 0.74 in 75 infertile patients (Fanchin et al. 2003).
Several other studies have researched the capacity of AMH to predict ovarian response and the chance of a pregnancy. Tremellen et al. (2005) concluded in a study in 87 women undergoing IVF that AMH assessments are superior to FSH in identifying women with reduced ovarian reserve compared with women with a normal reserve.
Penarrubia et al. (2005) found in studying 80 women, that AMH concentrations obtained early during ovarian stimulation under pituitary suppression for assisted reproduction are better predictors of ovarian response than basal measurements of AMH.
Hazout et al. (2004) demonstrated a strong association between day 3 serum AMH levels and the number of mature oocytes, the number of embryos and clinical pregnancy rates in 109 IVF patients.

Muttukrishna et al. (2004) also found in a study in 69 IVF patients that compared with FSH and Inhibin B, AMH is the best single marker of ovarian response to gonadotrophin stimulation in terms of number of women with poor response and number of eggs collected in IVF cycles.
Van Rooij et al. (2005) have shown in a longitudinal study of 81 patients who were followed for about four years that AMH is a fairly good endocrine marker for the age-related decline of reproductive capacity.

In conclusion, although AMH is correlated with ovarian reserve and hence candidate for use as a predictor, its predictive capacity is too limited to be of clinical value. Only the number of oocytes during egg retrieval and the number of embryos, but not the chance of a pregnancy could be predicted.

So in contrast to the stimulation phase, the implantation phase remains more or less a black box. Clinicians seem unable to influence the outcome in this phase, as they are grossly unaware of the mechanisms involved. One of the rare factors that was found to be related to pregnancy after the implantation phase was embryo quality. Embryo quality might be affected by oxidative stress (Agarwal et al. 2005), but even morphologically normal embryos could show an abnormal number of chromosomes and low pregnancy rates (Twisk et al. 2006).

In the sparse literature on this topic it was reported that AMH at the time of HCG administration was positively correlated with the embryo score (Silberstein et al. 2006). Our observation that basal AMH is not related to embryo quality could contribute to an explanation for the low correlation with pregnancy probability, as embryo quality is crucial for clinical success (Schmidt et al. 2005).
These seemingly contradicting findings might be explained by the different assessment points during treatment, stressing the fact that additional research is needed.

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4

Follicle-stimulating hormone isoforms are not useful as pretreatment predictors of outcome in in vitro fertilization: a pilot study

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Abstract

The objective of this study was to determine the predictive value of FSH-isoforms for the outcome of IVF treatment. Although this pilot study comprises only a small number of patients, we conclude, since no statistical differences could be found in the isoform-composition between poor and good responders, that it is not likely that FSH-isoforms predict treatment outcome after IVF.

Introduction

In in-vitro fertilization (IVF) programmes, treatment outcome is highly variable and difficult to predict. Ovarian responsiveness to gonadotropins and number and quality of embryos after fertilization still is unpredictable. However, to be able to optimise patient counselling and make best use of restricted resources, the search for predictors of treatment outcome is still ongoing (Templeton et al. 1996, Stolwijk et al. 1996). Unfortunately it is still not possible to create a model to predict treatment outcome accurately (Smeenk et al. 2000).

Follicle-stimulating hormone (FSH) is the most frequently studied basal hormonal predictor, assessed before pituitary down-regulation. It was reported to have additional predictive value or even better predictive value than age alone (Muasher et al. 1998). On the other hand, Bancsi et al. (2003) concluded in a meta analysis that the clinical value of testing basal FSH concentrations is restricted to a minority of patients. Recently Hendriks et al. (2005) concluded that antral follicle count might be considered the test of first choice in the assessment of ovarian reserve prior to IVF.

FSH is a heterodimer composed of an alpha and beta-subunit with glycosylation sites located on each of the subunits. The oligosaccharide attached to the FSH molecule terminates in a negatively charged residue, thereby forming a variety of isoforms which differ in their isoelectric points. The acidic isoforms were found to have a reduced bioactivity as assessed by its potency to stimulate cyclic AMP production and a longer half-life time in the circulation compared to the less acidic isoforms (Baird 2001; Lambert et al. 1998).

The distribution of FSH isoforms in blood varies throughout the menstrual cycle and during life (Anobile et al. 1998). There is increasing evidence that the extent and pattern of glycosylation is under hormonal control (Ulloa-Aguirre et al. 1988). It was suggested that different glycoforms may encode for different functions or have enhanced activity for a particular function (Padmanabhan 1995).

Oestradiol concentrations were associated with less acidic FSH glycoforms during the menstrual cycle. The menopause oestrogenic loss was found to result in acidic, relatively simple glycoforms (Anobile et al. 1998). Similar findings were reported by Flack et al.(1994) and Creus et al.(1996).

Since the growth of antral follicles is totally dependent on FSH, it was hypothesized that not only the quantity but also the quality of FSH, in terms of isoforms plays an important role in the early follicular phase. In a recent discussion it was suggested that the FSH isoform composition of commercial gonadotropin preparations is of clinical importance and should be taken into account when evaluating treatment efficacy (Andersen et al. 2004), which further underlines the independent role of FSH isoforms.

In our clinic FSH is the only clinically meaningful hormonal predictor. Women with high pre-treatment levels of FSH (> 10 IU) are treated with increased dosages of gonadotropins and patients older than 41 years of age are not treated at all. Since the sensitivity of FSH levels in predicting a poor response was low, we hypothesized that the acidity of the FSH could provide valuable additional information on the prognosis of patients, which we would miss by just regarding the concentration of total FSH-immunoreactivity.

The aim of this study was therefore to assess the role of FSH-isoforms with respect to treatment outcome of the IVF procedure.

Materials and methods

Patients and treatment

A total of 156 women started their first cycle of IVF treatment. The IVF protocol was similar for all patients. In all patients both ovaries were present. The treatment consisted of a long protocol of pituitary down-regulation with an agonist (Decapeptyl®, Ferring, Hoofddorp, the Netherlands) starting at day 21 of the previous cycle, followed by ovarian stimulation with recombinant human gonadotrophin (Puregon®, Organon, Oss, the Netherlands).

Oocyte retrieval by transvaginal ultrasound-guided puncture was performed 36 h after human chorionic gonadotrophin (Pregnyl®, Organon, Oss, the Netherlands) administration. Forty-eight hours after ovum retrieval and fertilization, no more than two embryos were transferred into the uterine cavity and this was followed by luteal support with Progestan® (Organon, Oss, the Netherlands). According to the protocol, young patients received a fixed daily dosage of 150 IU and older patients (over 37 years) received a fixed dosage of 300 IU recombinant FSH daily.

For reasons of efficiency and costs, the present pilot study comprised two groups of five women. Two homogenous but clearly distinct groups were selected to

investigate additional predictive value of the FSH-isoforms. Inclusion criteria of the response and poor response group comprised age (young versus significantly older), response to FSH treatment (150 IU versus 300 IU), and outcome (pregnancy versus no pregnancy) of the IVF treatment. Patients were screened on day 3 of the cycle preceding the IVF-treatment cycle.

The following data were collected: age, body-mass index (BMI), serum FSH concentration and antral follicle count (AFC). Serum was obtained and stored at minus 20 degrees Celsius until further processed.

Outcome variable was the number of oocytes. Poor response was defined as less than 4 follicles of 15mm or more, during stimulation.

Determination of FSH isoforms

A fast performance liquid chromatography (FPLC) sytem (Pharmacia) equipped with a 4 ml Mono-p column was used for chromatofocusing of FSH to determine its isoforms. To exchange the storage counter ion of the column the resin was washed with 2 ml of a 2M NaCl solution and then equilibrated at a flow rate of 0.5ml/min with 30-50ml starting buffer (7.14 mM bis-tris, pH 7.3-7.4) until the effluent pH was equal to that of the starting buffer. The 2.5-ml serum specimens were desalted on a PD-10 column (Pharmacia), degassed, eluted with bis-tris starting buffer and made up to 10 ml with this buffer. Next, 8.5 ml of the sample was loaded onto the column and the pH gradient generated by introducing the Polybuffer 74 (Pharmacia) elution buffer at a flow rate of 0.5 ml/min. One-hundred-forty 1-ml effluent fractions were collected and pooled at a pI < or > 4.3, defined as a relevant pH cut-off point (9). The lowest detectable concentrations (0.15 IU/L) of FSH fell within the working range of the FSH immunoassay (AxSYM, Abbott) and mean recovery from the Mono-P column varied between 94 ± 8.5 (SD) % and 97 ± 4.2 (SD) %. The acicity of FSH-isoforms was expressed as a ratio of the proportion of isoforms with pH>4.3/the proportion of isoforms with pH<4.3

Statistical analysis

Non parametric chi-square tests were used to compare groups. Significant differences were defined as a p-value <.05.

Informed consent was obtained from all participants. This study was approved by the ethical committees of the institution. All participants were guaranteed confidentiality, and only the principal investigator (JS) had full access to the data.

Results

The 'responder' group of women (mean (SD) age: 30.8 (2.1)) had a normal FSH concentration, a good response to gonadotropins (and pregnant) after the first treatment cycle. The 'poor responder' group of women (mean (SD) age:38.6 (1.5)) had also normal FSH concentrations, with a poor response to gonadotropins, and consequently did not become pregnant after the first treatment cycle.

The table depicts the pre-treatment variables of the groups of responders and non-responders. Serum FSH, FSH isoforms and serum inhibin B were determined.

Table I: Pretreatment variables (mean (SD)) in responders and non-responders

	Responders	Poor Responders	P-value
BMI	24.0 (1.6)	24.9 (5.8)	.69
Antral Follicle Count	7.2 (1.4)	3.4 (1.8)	.01
FSH	5.1 (1.5)	5.3 (1.6)	.84
FSH isoform ratio	1.3 (1.0)	0.9 (0.3)	.44
Inhibin B	94.8 (11.5)	22.0 (13.8)	.00

Responders and poor responders statistically differ in antral follicle count and Inhibin B concentrations in blood, but no pretreatment differences were found regarding FSH concentrations in blood and FSH-isoform ratios.

Discussion

In the present study FSH-isoforms were investigated in order to study their predictive value with respect to the response to gonadotropins in IVF/ICSI treatment.

No statistical differences were found in the FSH isoform ratio between responders and poor responders to FSH treatment, suggesting no clinical relevant role of FSH-isoforms to predict the outcome of IVF treatment. Our study appeared to show presence of more acidic and complex isoforms in the responder group of young women, but this difference did not reach statistical significance.

Several authors provided data suggesting different biological functioning of different FSH-isoforms. However, the literature data are not unequivocal. West *et al.* (2000) showed that more acidic FSH isoforms are better facilitators of follicular maturation and increased estradiol production than less acidic isoforms. However, Andersen et al. (2001) showed that less acidic isoforms were found to be twice as effective as the acidic isoforms in the production of cAMP in oocyte cumulus complexes from large preovulatory follicles.
Furthermore, resumption of meiosis was found to be significantly more efficient if induction was performed with less acidic isoforms from the circulation (Andersen et al. 1999). Antonio et al. (1999) found a faster clearance of less acidic isoforms compared with the more acidic isoforms. Less acidic isoforms exhibited a higher in-vitro biopotency than the acidic isoforms. Vitt et al. (1998) found that the least acidic isoform induced the fastest preantral growth, the largest antral follicles and had more impact on stimulation of estradiol production and antral formation than the more acidic isoforms.
Next, in sheep, age and reproductive state were found to be associated with the forms of FSH that were extracted from the pituitary gland. Qualitative changes in FSH were found to be important in the physiological regulation of follicle turnover (Cooke et al. 1997).
In short, more acidic FSH isoforms have a slower clearance from the circulation and consequently a longer half-life, but have a lower bioactivity compared with less acidic FSH isoforms.

In our study Inhibin B concentration and antral follicle count, two known predictors of poor response significantly differed between the responders and the poor responders. FSH isoforms do not provide us additional information upon the response to gonadotropins. Although this could be due to stratification of the groups using a normal basal FSH concentration and age and to the limited sample size.

No evidence can be provided that qualitive information on the FSH-isoforms predicts the ovarian response during IVF treatment.

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Part II

Integration of psychological and biomedical factors in IVF

5

The effect of anxiety and depression on the outcome of in-vitro fertilization

Human Reproduction 2001; 16: 1420-1423

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Abstract

Objective: This study aimed to clarify the role of depression and anxiety on the outcome in assisted reproductive treatment. Previous studies on this topic have shown contradicting results, which may have been caused by population characteristics, the design of the study, or small sample sizes.

Methods: In a multicentre prospective study 281 out of 359 (81%) consecutively invited women were willing to take part. Before down-regulation by means of GnRH-analogues in a long IVF-protocol, patients were asked to fill out the Dutch version of the State and Trait Anxiety Inventory to measure anxiety and the Dutch version of the Beck Depression Inventory (BDI) to measure depression. Multiple logistic regression analysis was used to analyse known predictors of pregnancy and psychological factors and their relation with treatment outcome.

Results: We showed a significant relation between base-line psychological factors and the probability to become pregnant after IVF treatment, controlling for other factors. State anxiety had a stronger correlation with treatment outcome than depression.

In conclusion: pre-existing psychological factors are independently related to treatment outcome in IVF/ICSI and should therefore be taken into account in patient counseling. Psychological factors may be improved by intervention, whereas demographic and gynaecological factors cannot. Future studies should be directed towards underlying mechanisms involved and the role of evidence based distress reduction in order to improve treatment results.

Introduction

Women undergoing in vitro fertilization (IVF) treatment are often anxious and depressed because of their infertility and the uncertainties of the treatment they have to deal with (Mahlstedt 1985). Indeed epidemiological and anecdotal data suggest a relationship between psychological factors and infertility (Freeman et al.1985; Lapane et al. 1995). However, a systematic review of controlled studies before 1990 presented contradicting results (Wright et al. 1989). More recently, a review by Eugster and Vingerhoets (1999) indicated that the influence of psychological factors on the outcome of IVF/intra cytoplasmatic sperm injection (ICSI) still continues to be a matter of debate. In this review no particular attention to ICSI was paid. Prospective studies using standardized psychometric tests are scarce and results are difficult to compare (Boivin and Takefman 1995; Demyttenaere et al.1992, 1998; Merari et al. 1992; Thiering et al. 1993). The somewhat inconsistent findings in these studies may be due to population characteristics, the design of the study, or small sample sizes. Moreover, multi-centre studies are preferable because predictions have the tendency to be centre-specific.

It still has to be established what the role of psychological factors in IVF/ICSI outcome is. As this knowledge is a prerequisite for adjuvant psychological interventions, the question has a major clinical relevance.

Several statistical models have been published using combinations of biomedical factors in relation with IVF outcome. The model of Templeton is well known; it is based on a large database and includes the factors age, duration of infertility, number of previous unsuccessful IVF attempts, tubal indication for fertility treatment and number of previous pregnancies as independent predictors (Templeton et al.1996). Stolwijk et al. (1996) identified two factors, i.e. at least two preceding gestations and age, to be significant in predicting IVF-outcome. It was also demonstrated that both models have limited external validity (Stolwijk et al. 1996; Smeenk et al. 2000). A possible reason for the limited validity of the presented models is that they are only based on stable variables. Some studies, however, indicate that the success of assisted reproductive techniques (ART) treatment may also be dependent on variable factors, such as a woman's distress level at the time of treatment (i.e. Boivin & Takefman 1995; Demyttenaere et al. 1998; Fachinetti et al. 1997). The main objective of the present study at three

Dutch hospitals was to clarify the additional role of pre-existing anxiety and depression on IVF/ICSI results, controlling for known predictors.

Materials and Methods

All patients who went to the University Medical Centre St. Radboud Nijmegen, an academic tertiary referral centre in the east of the Netherlands and to two hospitals of Breda (Baronie and St. Ignatius), secondary referral hospitals in the south-west of the Netherlands, for the first cycle of a new IVF/ICSI treatment between January 1999 and March 2000, were invited to participate in the study. A long protocol with Decapeptyl® (Ferring, Hoofddorp, the Netherlands), Puregon® (Organon, Oss, the Netherlands) and Pregnyl® (Organon, Oss, the Netherlands) was used. Only first treatment cycles of a three-cycle course of IVF/ICSI were included. A maximum of two embryos was transferred per treatment cycle, three days after ovum pick up (OPU). Remaining embryos of good quality were cryopreserved. Between cycleday 10 and 20 of the cycle before the stimulation cycle, so before the start of GnRH-analogue medication, women were asked to complete questionnaires on psychological factors and return it in a pre-paid envelope to the hospital. All participants were guaranteed of anonymity and a separation of questionnaire information and their clinical management. Signed informed consent was obtained from all participants. The study was approved by the Ethical Committees of the hospitals in Nijmegen and Breda.

Of the 359 invited patients (313 in Nijmegen, 46 in Breda), 68 declined or were excluded. Reasons indicated by patients were: lack of time (twenty-three), already participating in another study (seven), emotional burden of the treatment (seven), unknown (five). Twelve patients were excluded because of missing data and fourteen because of language difficulties. Therefore, the remaining group consisted of 291 (81%) patients.

The demographic and gynaecological variables studied are derived from the model of Templeton; age, duration of infertility, number of previous pregnancies and infertility diagnosis. In addition to 'tubal' factor as diagnosis as in Templeton's model, other infertility diagnoses were included. Since only the first cycle of each patient was included, number of previous unsuccessful IVF-attempts was not included as a predictor.

Anxiety was measured by means of the Dutch version of the State and Trait Anxiety Inventory (STAI; Spielberger, 1970; Dutch version by: VanderPloeg et al. 1980), a scale showing satisfactory reliability and validity. Trait anxiety refers to a general tendency of an individual to be anxious, whereas state anxiety refers to the anxiety level of an individual at a given moment. Both measures include 20 items, the score for each item ranging from 1-4, higher scores indicating more anxiety. Total scores range from 20 to 80. Coefficient alpha for state anxiety in our sample was 0.94 and for trait anxiety 0.91.
Depression was measured by means of the Dutch version of the Beck Depression Inventory (BDI), (Beck et al. 1976; Dutch version by: Bouman et al. 1985) being one of the most widely used instruments for assessing intensity of depression and for detecting depression in the general population. This reliable and valid measure (Beck et al. 1988) includes 21 items, the score for each item ranging from 0 (low) to 3 (high). Total scores range from 0 to 63. Coefficient alpha in our sample was 0.86. Because of high levels of curtosis and skewness on the BDI scale, square roots were taken from the scores and used in the analysis (Tabachnick et al. 1996).

The outcome measures were the number of follicles, number of embryos and pregnancy status. The number of follicles was defined as the number of follicles (≥ 9mm) present on trans-vaginal-ultrasound, on the day of human chorionic gonadotropin (HCG) administration. Pregnancy was defined as a positive urinary pregnancy test 15 days after embryo transfer. In our analysis we focussed on the women who reached embryo transfer because we wanted to be able to compare all stages of treatment, including the implantation phase.

All statistical analyses were performed by means of the SPSS-program. Multiple logistic regression analysis was used to analyse the variables related to pregnancy. The first step was, by using a backward conditional stepwise procedure, to find biomedical variables from Templeton's model related to treatment outcome in our sample. The second step was to add psychological variables to this block of variables, again in a stepwise backward procedure. Linear logistic regression techniques were used to compare outcome variables between groups and T-tests were used to compare groups on baseline parameters.

Results

The patients (n=291) categorised the cause of infertility themselves as follows: female factor 25%, male factor 42%, combined male and female 9% and idiopathic 24 %. Thirty-six percent (n=85) of the cycles, diagnosed as 'male factor only', were ICSI cycles. Thirty-five percent reported one or more previous pregnancies, 19% reported one or more previous abortions and 26% reported one or more previous live births, of which nine percent resulted from a previous IVF/ICSI attempt. The state-anxiety (t=.52, p=.61) and the BDI-depression scores (t=1.40, p=.16) did not differ between Nijmegen and Breda. The trait anxiety, however, was significantly lower in Breda (t=2.10, p=.04). The state and trait anxiety levels, as well as the depression level of our IVF/ICSI population lie within the normal range, as compared with a community sample, which is consistent with previous publications (Freeman et al. 1985; Hearn et al. 1987; Reading et al. 1989).

From the original group of 291 women, 237 (81%) women reached embryotransfer. Reasons for not reaching embryotransfer were cancellation by patient (n=4), poor response (n=19), risk of ovarian hyperstimulation syndrome (n=5) or total fertilization failure (n=26). The group who did not reach embryotransfer (N=54) was the same age (t=.97, p=.34) as the group who did reach embryotransfer. In addition no differences in state anxiety (t=.59, p=.56), trait anxiety (t=.14, p=.89) and depression (t=1.38, p=.17) scores were found. Sample characteristics with respect to demographic and psychological variables of the group that reached embryotransfer are shown in Table I.

Table I: Characteristics of the group women who reached ET (N=237)

	Mean	SD	Range	Median
Age (years)	33.4	3.7	24-42	33
Duration of infertility (years)	3.7	2.0	1-13	3
State anxiety score	37.3	9.6	20-74	36
Trait anxiety score	36.8	8.3	20-63	35
BDI score	5.6	5.1	0-20	4

The regression analysis with only biomedical variables shows that higher age and lower number of previous pregnancies were correlated with poor outcome (Table II). Duration of infertility and the diagnostic category were excluded from the equation due to a lack of correlation with pregnancy in the analysis.

Table II: The logistic regression model with biomedical variables

Variable	B	Wald Statistic	P value	95% CI
Age	-0.10	5.66	.02	(-.17, -.02)
Previous Pregnancy	0.55	4.10	.04	(.02, 1.08)
Constant	2.72	4.04	.04	

Model characteristics:

-2 Log Likelihood = 289,8

Goodness of Fit = 221,0

R^2 = .04

Chi-Square 7.4 ; p-value = .02

Variables not in the equation with p-values between brackets. [Residual Chi Square 3.4, p=.64]

Duration of Infertility (.77), diagnosis: female factor (.67), diagnosis: male factor (.22), diagnosis: combined female/male (.70), diagnosis: unknown (.14)

In Table III the model is depicted after adding psychological factors to the model with the two biomedical variables. The trait anxiety score and the depression score were left out from the equation due to a lack of correlation with pregnancy in the analysis.

Table III: Logistic model with biomedical variables and psychological variables

Variable	B	Wald Statistic	P value	95%CI
Age	-0.12	7.65	.01	(-.21, -.03)
Previous Pregnancy	0.66	5.40	.02	(.10, 1.21)
State anxiety	-0.04	5.99	.01	(-.06, -.01)
Constant	4.84	9.35	.002	

Model characteristics:

-2 Log Likelihood = 278.8

Goodness of Fit = 219.5

R^2 = .10

Chi-Square 16.34 ; p = .001

Variables not in the equation with p-values between brackets. [Residual Chi Square 1.5, p= .48]

BDI (.23), Trait anxiety (.62)

The model showed a significant independent negative relation of state anxiety with pregnancy. The variable depression did not enter the model because it had a high correlation anxiety (r=0.70) with state anxiety. In a model with age, number of previous pregnancies and depression only, depression proved to have an independent and significant negative correlation with pregnancy (p=.03) as well. Therefore, we repeated the analysis using the 'composite' score, in which the standardised scores of state anxiety and depression were summed. The results of this final model are depicted in Table IV.

Table IV: Logistic model with biomedical variables and the composite score of state anxiety and depression

Variable	B	Wald Statistic	P value	95%CI
Age	-0.12	6.30	.01	(-.21, -.03)
Previous Pregnancy	0.82	7.19	.01	(.10, 1.21)
Composite score	-0.17	7.66	.01	(-.26, -.05)
Constant	3.27	4.74	.03	

Model characteristics:

-2 Log Likelihood = 245.1

Goodness of Fit = 196.7

R^2 = 0.12

Chi-Square 18.53 ; Significance .003

To look for the stage of treatment in which the effect of state anxiety on treatment outcome is most obvious, we compared the outcome variables of various stages

during treatment. Linear regression revealed no relation of age, number of previous pregnancies and state anxiety with the number of the follicles (b=-.14, p=.14; b= -.05, p=.49; b=-.06, p=..37 respectively), oocytes (b=-.12, p=.09 ; b=-.04, p=.56; b=-.06 , p=.41), or embryos (b=-.14, p=.06; b=.06, p=.37; b=-.02, p=.75). Our data show that the stimulation and the fertilisation phase were not influenced, whereas the pregnancy rate was influenced.

Discussion

This study showed a significant relation of psychological variables with pregnancy in IVF/ICSI-treatment. Adding the composite score of state anxiety and depression to the model improved the model significantly and led to the best prognostic model with respect to pregnancy. The analysis showed that state anxiety only is a better predictor of pregnancy than depression.

In addition we found an independent relation of 'age' and 'number of previous pregnancies' with the probability to become pregnant, which is consistent with previous findings (Stolwijk et al. 1996). Other variables presented in the model by Templeton et al. (1996) did not show a significant relation with treatment outcome, stressing once more the limited external validity of the Templeton model. Our data are in line with a study by Fachinetti et al. (1997) in which effects of state anxiety and not trait anxiety on ART outcome were found. Demyttenaere et al. (1992) also found a negative influence of state anxiety on IVF outcome, but did not publish on trait anxiety.

Thiering et al. (1993) found significantly lower success rates in IVF in depressed versus non-depressed women, but could not demonstrate a predictive value of the anxiety. Several authors, however, found no relation between the emotional status of women and the outcome of ART treatment (Ardenti et al. 1999; Boivin & Takefman 1995; Harlow et al. 1996; Slade et al. 1997).

Though the power of our study was good and the study was multicentred in design, it would be recommendable to reproduce the findings in a larger group and validate the model in another population. Moreover, as the number of co-variables is limited to those found in the Templeton model and the fact that logistic regression cannot establish the exact relationship among variables, causal inference should be made cautiously. Finally we cannot exclude the possibility of selection bias, as some patients indicated 'stress' as a reason not to participate.

The mechanism of the distress effect on pregnancy rates is still unknown. Subtle disturbances of the cycle may play a role, which are caused by subtle endocrinological alterations (Psech et al. 1989; Demyttenaere et al. 1989, 1994). In a prospective study in women undergoing IVF an increase during treatment in state anxiety was established, parallel to increases in serum prolactin and cortisol (Harlow et al. 1996). Depression was found to be associated with an abnormal regulation of luteinizing hormone (Meller et al. 1997).

Some studies suggest promising results of psychological interventions on pregnancy rates (Domar et al. 1990, 2000; Sarrel & DeCherney 1985). Further prospective research is needed to obtain a better understanding of the mechanisms involved and provide an evidence base for effective stress reduction interventions aiming at better pregnancy rates.

In conclusion, our study shows that state anxiety may have an independent contribution to explaining the variability in pregnancy rates in addition to some well known biomedical variables. This effect is probably strongest in the implantation phase of the cycle. These findings are particularly important because in contrast to, for example, the factor age, psychological factors may be well sensitive to interventions, thus increasing the chance of improving treatment results. In view of our results, psychological factors should be taken in consideration in patient counseling.

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6

Reasons for dropout in an In vitro fertilization/Intra cytoplasmatic sperm injection program

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Abstract

Objective: The aim of the present study was to gain more insight into psychological aspects of dropping out in IVF/ICSI.
Design: Prospective cohort study.
Setting: University hospital-based tertiary care fertility clinic.
Patient(s): Women entering their first treatment cycle of IVF or ICSI.
Intervention(s): Standardized psychological questionnaires were administered before the start of the treatment and after treatment.
Main Outcome Measure(s): Reasons for dropout, state and trait anxiety, depression, marital and sexual satisfaction
Result(s): Base-line psychological factors and the probability of dropout after IVF/ICSI treatment were found to be associated in the group that stopped treatment for psychological reasons. Those who were denied further treatment by the medical team, the 'actively censored' group, did not show pretreatment differences regarding psychological measures in comparison with those who continued treatment. After treatment, the group that was denied further treatment showed higher levels of anxiety and depression compared to those that continued.
Conclusion(s): Dropout, being a well-known phenomenon in IVF/ICSI, is related to pre-existing psychological factors in IVF/ICSI. Actively censored patients were psychologically well adjusted before treatment, but this changed after censoring.

Introduction

High dropout rates are a common phenomenon in IVF/ICSI treatment (De Vries et al. 1999, Land et al. 1997, Osmanagaoglu et al. 1999, Roest J et al. 1998, Stolwijk et al. 2000, Goverde et al. 2000, Emery et al. 1997). Dropout may be considered as an adverse treatment outcome. The prognosis of a couple and thereby the effectiveness of the program, in terms of cumulative pregnancy rates, is strongly influenced by selective early cessation. Discontinuation of treatment may have various reasons and dropouts can be categorized as 'actively' and 'passively' censored (Land et al. 1997). 'Actively censored' patients are those who are denied further treatment because of a poor prognosis (physician recommended dropout). 'Passively censored' patients are those who discontinued treatment voluntarily.

Reasons for dropout have been scarcely investigated until now. However, in retrospective studies several reasons were identified; psychological, financial, relational and practical reasons, but also denial of further treatment, other medical problems, other treatment options, fears regarding the complications of the procedure and treatment-independent pregnancy (Land et al. 1997, Osmanagaoglu et al. 1999). Emotional stress was already found to be the second (after financial) most influential factor leading to the couple's decision not to pursue treatment (Goldfarb et al. 1997). The age of the husband and being a mother or not were found to related to the decision to continue treatment or not. But age of the woman, duration of infertility and number of IVF attempts were not found to be related to the decision (Callan et al. 1988).

The aim of the present study was to gain more insight into the psychological and biomedical considerations for dropping out in IVF/ICSI in a prospective manner. We hypothesized that (I) pretreatment psychological and marital and sexual aspects play an important role in couples who are passively censored, (II) actively censored patients show increased levels of anxiety and depression after censoring after controlling for treatment outcome. As a result, we might be able to early identify the couples prone to drop out or at risk for developing psychological problems.

Materials and Methods

Sample

Data were used from couples who came for the first cycle of a new IVF/ICSI treatment, at the University Medical Centre Nijmegen, The Netherlands, between

January 1999 and May 2000. This group participated in a prospective follow-up study on the psychological aspects of IVF/ICSI treatment. Details of the program and the applied protocol were described previously (10). Four-hundred-and-fifty couples were contacted and 380 (84%) were willing to participate. Participants were asked to complete questionnaires on psychological factors two weeks before the start of treatment (T1) and four weeks after the first treatment cycle (T2), once the pregnancy test result was known.

All participants were guaranteed confidentiality and a separation of the questionnaire information on psychological, marital and sexual factors and their clinical management. Written informed consent was obtained from all participants.

Couples were included in the study as soon as they were called on to start the first treatment cycle. They were observed until an ongoing pregnancy was determined, or discontinued treatment. The follow up period was at least 12 months after the first and (if applicable) after the second completed IVF/ICSI cycle. Dropouts were defined as the group of patients who stopped treatment after an IVF/ICSI cycle, in which they failed to achieve an ongoing pregnancy. In order to actualize the waiting list, patients who failed to contact the team for more than 12 months after a failed cycle were contacted to determine whether they had withdrawn from treatment. Reasons for withdrawal were recorded. If patients indicated that they wanted to stay on the waiting list, they were classified as having postponed treatment. Patients who could not be contacted, for instance after moving without giving notice, were considered lost for follow up.

An ongoing pregnancy was defined as a positive heartbeat on transvaginal ultrasound, five weeks after embryo transfer. If a woman would turn out not to be pregnant, the cryopreseration-thaw cycles, if applicable, were being done directly after the treatment cycle in which the embryos were obtained. An attempt was therefore defined as the initial cycle and the cryopreservation-thaw cycle(s) resulting from this cycle. The pregnancies resulting from cryopreservation-thaw cycles were included in the overall pregnancy results.

A maximum of three completed attempts was included in the study. Since health insurance institutions in the Netherlands compensate three IVF/ICSI attempts, financial reasons for dropout could be excluded. Poor prognosis as the reason for active censoring was defined as poor response to high dosages of recombinant FSH (< 4 oocytes) and poor fertilisation (< 5% of the oocytes fertilized by ICSI in the case of ≥ 4 oocytes) (Smeenk et al. 2001).

In case of passive censoring, the patients indicated their main motives for discontinuation during a visit at our outpatient ward to evaluate the preceding treatment cycle. Sometimes, patients only informed the team by phone of their decision. The reasons for discontinuation were categorized based upon the couple's motives and the interpretation of the consult at the outpatient ward by the physician. This was documented in the medical file.
If an IVF/ICSI attempt was converted to an intra-uterine insemination (IUI) due to poor response, or stopped due to complaints of the ovarian hyperstimulation syndrome (OHSS), the IVF/ICSI attempt was considered to have failed.
Pregnancies that did not result from an IVF/ICSI attempt were classified in the passively censored group, which included pregnancies resulting from an IUI procedure.

Psychological measures
Anxiety was measured by means of the Dutch version of the State and Trait Anxiety Inventory (Spielberger et al. 1970), a scale showing satisfactory reliability and validity. Trait anxiety refers to a general tendency of an individual to be anxious, whereas state anxiety refers to the anxiety level of an individual at a given moment. Both measures include 20 items, the score for each item ranging from 1 to 4, with higher scores indicating greater anxiety. Therefore the total scores range from 20 to 80.
Depression was measured by means of the Dutch version of the Beck Depression Inventory (BDI) (Beck and Beamesderfer 1976). This scale is one of the most widely used, reliable and valid instruments for assessing intensity of depression and for detecting depression in the general population. This measure includes 21 items, the scores for each item ranging from 0 (low) to 3 (high), therefore the total scores range from 0 to 63. Square roots were taken from the scores to obtain a normal distribution.
Relational aspects were measured by means of two scales of the Maudsley Marital Questionnaire (MMQ). The scores can be reduced to: a scale to assess relational (10 items, range 0-80) and sexual (dis)satisfaction (5 items, range 0-40) (Spielberger et al. 1970). Higher scores indicate greater dissatisfaction (Arrindell et al. 1983).

Demographic factors
Age and duration of infertility were compared between the groups.

Statistical analysis

All statistical analyses were performed by means of the SPSS-program. One-way analysis of variance (ANOVAs) with Dunnett posthoc tests were used to compare groups. So the resulting p-values were calculated after Dunnett posthoc tests. Kruskal-Wallis tests were used to compare the subgroups in which the reasons for passive dropout were compared, since these data were not normally distributed. Multiple logistic regression was used to analyze the variables related to dropout. In a backward elimination procedure the best predictor with respect to dropout was identified.

In view of our hypothesis, patients who discontinued treatment due to passive censoring after the first and second cycle were compared with those who continued treatment. Furthermore, the patients who stopped treatment due to active censoring were also compared with those who continued treatment. The pretreatment anxiety and depression, the quality of the relationship with the partner and demographic factors were taken into consideration.

Results

Three-hundred-and-eighty women (84% of all invited women) completed the first set of questionnaires (T1). Two-hundred-and-forty out of 380 (63%) completed the second set of questionnaires as well (T2). The women underwent a total of 748 cycles, 62% being IVF and 38% being ICSI cycles. In the first cycle, 28 cycles were converted into IUI procedures and four cycles were discontinued because of OHSS.

In the second cycle, 5 cycles were converted into IUI procedures. The majority of the women, 60%, reported primary infertility. The cause of infertility was categorized as: female only 23%, male only 40%, combined male and female 8% and idiopathic 29%.

Other baseline characteristics on pretreatment biomedical and psychological variables can be found in Table I.

Table I: Biomedical and psychological characteristics of the cohort (N=380)

	Mean	SD	Range	Median
Woman's age (years)	34.1	3.9	21-43	34
Duration of infertility (years)	3.7	2.2	1-16	3
State anxiety score	37.1	10.6	20-74	36
Trait anxiety score	37.2	8.5	20-63	36
Depression score	6.2	5.8	0-36	5
Relational dissatisfaction	9.8	7.3	0-42	8
Sexual dissatisfaction	7.6	6.1	0-38	6

Treatment characteristics of the cohort can be found in Table II. Four (11%) ongoing pregnancies resulting from 36 cryopreservation-thaw cycles were observed in the first treatment cycle, no pregnancies were observed in 13 cryo-cycles during the second cycle and in the third cycle two (18%) pregnancies was observed in 11 cryopreservation-thaw cycles.

Table II: Results of the first three IVF/ICSI cycles: pregnancy rates (PR) and dropout rates (DR)

	First cycle	Second cycle	Third cycle
No.of patients	380	237	135
No.of pregnancies	92	62	18
No.of dropouts	16 active (5.6%)	8 active (4.6%)	
(through censoring)	35 passive (12.2%)	32 passive (18.3%)	
PR per cycle	24.2%	26.2%	13.3%
(95% CI)	(19.9-28.5)	(20.6-31.8)	(7.6-19.0)
DR per cycle	17.7%	22.8%	
(95% CI)	(13.3-22.1)	(16.6-29.0)	

Dropout first treatment cycle

Psychological and demographic variables were compared between the passively and the actively censored group, separately, with the uncensored group. Details of these groups, regarding the first cycle can be found in Table III.

Table III: Comparison of baseline characteristics (mean(SD)) between groups of patients who were uncensored, passively censored and actively censored after the first treatment cycle

	Uncensored (0)	Passively Censored (1)	Actively Censored (2)	Post hoc tests
No. of patients	237	35	16	
Woman's age (years)	33.8 (3.8)	35.4 (3.7)	36.9 (3.7)	0<2; 1=2
Duration of infertility (years)	3.7 (2.1)	4.1 (2.5)	4.2 (3.7)	0=1=2
State anxiety score	36.3 (10.0)	42.5 (14.3)	39.7 (12.2)	0<1; 1=2
Trait anxiety score	37.0 (8.3)	39.6 (10.0)	37.8 (8.3)	0=1=2
Depression score	5.8 (5.3)	9.5 (8.7)	5.9 (6.0)	0,2<1
Relational dissatisfaction	9.8 (7.3)	10.5 (7.8)	8.8 (6.0)	0=1=2
Sexual dissatisfaction	7.7 (6.1)	8.2 (6.8)	6.2 (4.3)	0=1=2

The passively censored group during the first cycle showed higher scores pretreatment on depression (p=.00) and state anxiety (p=.00) than the group that continued treatment after the first treatment cycle. In the passively censored group the differences regarding demographic variables and other psychological measures did not differ significantly from those that continued treatment.
The percentages of the various reasons for passive censoring after the first treatment cycle can be found in Table V.

The actively censored group was characterized by higher age (p=.02), the duration of infertility did not differ significantly compared with those that continued treatment. No statistically significant differences regarding psychological, marital and sexual variables were found between the actively censored group and the couples who continued treatment.

Dropout second treatment cycle
Again psychological and demographic variables were compared between the passively and the actively censored group, separately, with the uncensored group. Details of these groups, regarding the second cycle can be found in Table IV.

Table IV: Comparison of baseline characteristics (mean(SD)) between groups of patients who were uncensored, passively censored and actively censored after the second treatment cycle

	Uncensored (0)	Passively Censored (1)	Actively Censored (2)	Post hoc tests
No. of patients	135	32	8	
Woman's age (years)	34.0 (4.0)	33.9 (4.0)	35.9 (3.6)	0=1=2
Duration of infertility (years)	3.7 (2.1)	4.1 (2.5)	4.2 (3.7)	0=1=2
State anxiety score	38.6 (10.3)	38.0 (12.4)	34.2 (11.9)	0=1=2
Depression score	6.9 (6.0)	5.3 (5.6)	5.8 (3.8)	0=1=2
Marital dissatisfaction	10.7 (8.2)	8.3 (6.2)	8.2 (6.8)	0=1=2
Sexual dissatisfaction	8.6 (6.4)	5.1 (5.8)	6.7 (5.8)	0=1=2

The passively censored group after the second cycle showed no significant differences with the uncensored group regarding any of the measures. The percentages of the various reasons for passive censoring after the second treatment cycle can be found in Table V

Table V: Reasons for passive censoring after the first and the second cycle

Reason for passive censoring	Dropout first cycle	Dropout second cycle
Psychological reasons	N=10 (29%)	N=7 (22%)
Other medical treatment	N=1 (3%)	N=6 (19%)
IVF/ICSI independent pregnancy	N=9 (26%)	N=4 (13%)
Fear of complications	N=9 (26%)	N=4 (13%)
Postponement/unknown	N=6 (17%)	N=11 (34%)

The actively censored group after the second cycle showed no statistically significant differences with the group that continued regarding age and duration of infertility. Lower scores were found on trait anxiety in the group that was actively censored (p=.04), but other measures did not differ significantly.

Analyses of subgroups

In order to obtain sufficient sample sizes, the subgroups who indicated the reason for passive dropout after the first and second cycle (in Table V) were combined. The subgroups were compared against each other on all psychological factors.

No statistically significant differences were observed in comparing the subgroups. Although the group that indicated psychological reasons to quit treatment (n=17) and the group that indicated fear of complications (n=13) showed the highest levels of anxiety and depression and the highest scores on the scales for marital and sexual dissatisfaction before treatment, these differences did not reach statistically significance.

Measurement at T2: after the first treatment

The results from the uncensored, censored active and the censored passive group with regard to anxiety and depression are depicted in figure I and II. Note that in the repeated measures design only complete data sets could be included. A significant group x time effect on depression (F=3.56; p=.03), but not on anxiety (F=1.35; p=.26) was found.

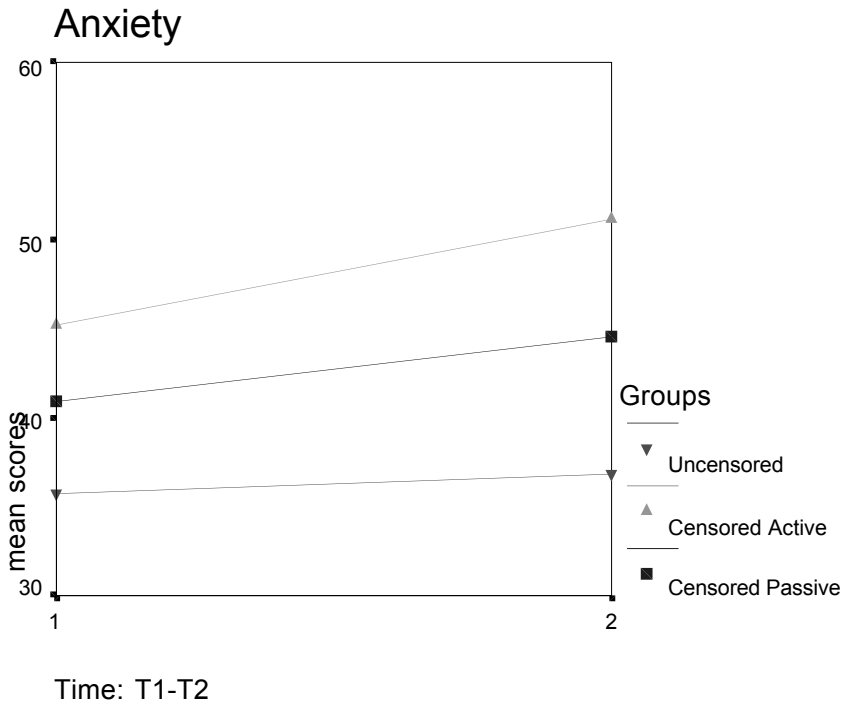

Figure I : Time effect of anxiety by way of censoring

In the figures I and II the significant increase in depression in the actively censored group is clearly shown. Unfortunately, a high refusal rate for ongoing participation in the study (50%) was found in this group.

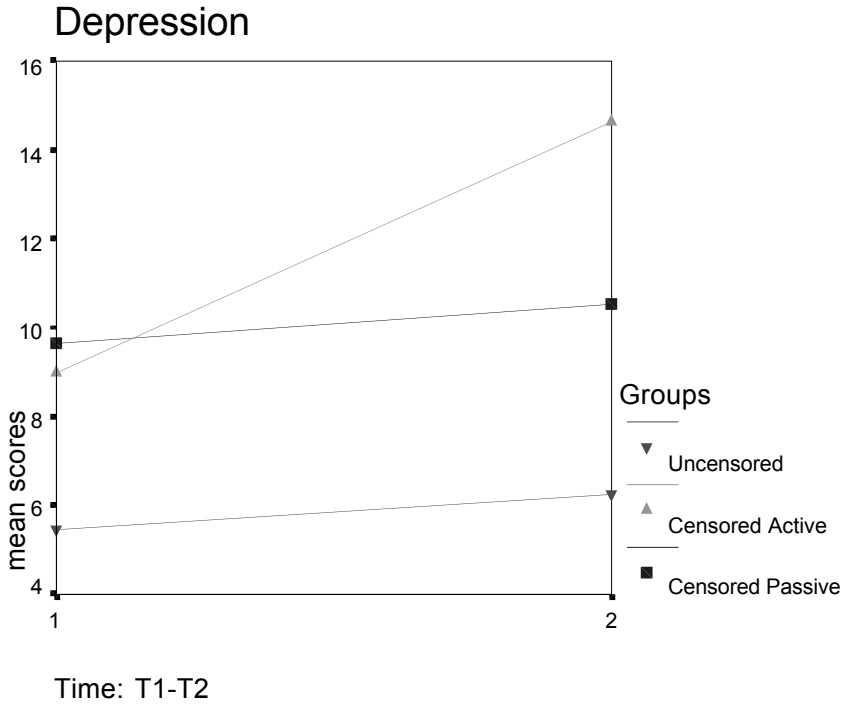

Figure II: Time effect of depression by way of censoring

Other increments in anxiety and depression in the various groups did not reach statistical significance. No significant differences could be found on marital and sexual aspects.

Clinical implications

In order to find the factor that was strongest correlated with passively censored dropout, a logistic regression of all available biomedical and psychological variables in a stepwise backward procedure was done. This revealed that pretreatment depression showed the strongest association with passively censored dropout (Chi=8.6, Beta=.085, Wald=8.60, p=.003).

The clinical implications were researched by dichotomizing the cohort in a group with scores indicative of moderate or severe depression (BDI ≥ 16) and a group with

BDI scores indicating mild or no depression (BDI<16) (Beck and Beamesderfer 1976). Based upon this dichotomisation a pretreatment 'depressed' group was identified in our sample (n=28). In this group a cumulative dropout rate of 35.7% was observed after three cycles. 29% of the depressed group (n=8) dropped out for psychological reasons.

Discussion

In this study we showed that passive dropout rates were related to psychological factors. Furthermore, we showed that marital and sexual aspects did not play an important role in passively censored couples. Actively censored patients were found to be significantly more distressed after the treatment than uncensored and passively censored women.

Dropout could not always be considered as an adverse treatment outcome, since 26% of the passively censored women reported a treatment-independent pregnancy after the first treatment cycle and 13% after the second treatment cycle. One could argue whether pregnancies that resulted from IUI cycles, after they were converted from IVF cycles, should be part of the passively censored group. Only a few pregnancies resulted from the IUI procedure, so the message remains that treatment independent pregnancies accounted for a considerable percentage of passively censored dropout.

Evers et al. (1998) reported on spontaneous pregnancies, especially occurring during the first three months on the waiting list for IVF/ICSI. It was suggested that this might be attributed to stress relief. In line with this hypothesis, initial treatment could have had the same beneficial effect and therefore be the explanation for the treatment-independent pregnancy rate in our sample.

The dropout group was a heterogeneous population, in which a clear distinction had to be made between the actively and the passively censored group. In our sample approximately 5% was actively censored per cycle due to poor response or poor fertilization during the treatment cycle. The actively censored group was characterized by higher age, however, not by a longer duration of infertility. The actively censored group did not differ psychologically from the uncensored group, although this changed after treatment. We found that active censoring led to significantly higher levels of depression.

This increase, but also the increase in anxiety, was particularly striking when compared with the uncensored and the passively censored group after an

unsuccessful treatment cycle. The actively censored group could therefore most likely benefit from psychological support in dealing with the outcome of treatment. The findings have to be interpreted carefully, since especially in the actively censored group, a high refusal rate for ongoing participation was observed. On the other hand, our findings could even underestimate the effect, since this refusal rate for ongoing participation could also be associated with higher levels of anxiety and depression.

In general, anxiety and depression were found to be increased after the first failed treatment (Sarrel et al. 1985). The passively censored group was characterized by higher scores on depression and state anxiety after the first cycle. No significant differences were found on other psychological measures and biomedical variables. This group showed no differences regarding any of the measures with the uncensored and actively censored group after the second cycle. Poor prognosis in terms of a different biomedical profile therefore did not seem to play an important role as a reason for dropout after the first or second treatment cycle. The findings suggest that the dropout group after the first cycle differed from the dropout group after the second cycle. Furthermore, we observed that the percentage of passively censored dropouts relatively increased with increasing cycle number.

No statistically significant differences were observed in comparing the subgroups of passively dropouts. Improved information could help especially these couples to develop realistic expectations and increase their ability to cope with the treatment.

For statistical reasons the dropout groups of the first and second cycle had to be combined. This limitation of the study could have masked the differences between the subgroups during the cycles. In the subset of the passively censored group after the first cycle that indicated psychological reasons for dropout we observed high levels of anxiety and depression. After the second cycle this could not be observed, which could be indicative of a selection process during the first treatment cycle. Once again this observation was based on small numbers, so careful interpretation is needed.

Another limitation of the study was that after the second cycle a large subgroup (34%) postponed treatment or was lost for follow up. Postponement of the last (financially compensated) cycle is a known phenomenon (Emery et al. 1997). Lost for follow up is more speculative; it could be due to logistical problems, but also intended by the couple.

Measures on marital and sexual aspects did not show significant differences between groups. This could be due to the fact that they did not play an important role in dropout. Whereas clinical experience seems to indicate that patients reporting psychological reasons for dropout, also reported difficulties in the relationship.
Previous research showed that a group of couples that did not pursue treatment felt that organized support groups could have been helpful to make IVF better or easier (Callan et al. 1988). Couples that dropped out due to passive and active censoring may benefit from psychological interventions in dealing with failed treatment. Moreover, since anxiety and depression were found to be negatively related to ongoing pregnancy rates in in-vitro fertilization (Smeenk et al. 2001), the overall prognosis of anxious and depressed women in the pretreatment phase could be defined as poor. Therefore, the pretreatment clinically depressed group could benefit most from psychological interventions from both a prognostic as a supportive point of view.

The decision to drop out of treatment is not easy to make for patients as well as for clinicians, and therefore the result of careful consideration. Clinicians can obviously hide behind protocols specific to their center or practical guidelines, whereas patients have to weigh their own pros and cons. Voluntary dropout may even be considered as a self-protective measure and from this point of view it is questionable whether we should try to prevent it. However, we believe that the couple's ability to face further treatment could be increased and as a result dropout rates could be decreased as a result from psychological interventions during treatment. Additionally, we believe that a substantial proportion of the passively censored couples could benefit from psychological interventions to cope more adequately with the failed treatment. Promising results of psychological interventions on pregnancy rates have been published (Domar et al. 2000, Boivin et al. 2003). Unfortunately, to our knowledge the effect of psychological interventions on dropout rates has not been studied. Further research on this particular aspect is needed to evaluate the clinical implications of our findings.

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Stress and outcome success in in-vitro fertilization: the role of self-reports and endocrine variables

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Abstract

Background: The aim of this study was to examine the associations between the stress hormones adrenaline, noradrenaline and cortisol in urine during treatment with the self reported stress, in order to investigate the mechanism for the previously observed negative association of anxiety and depression with the outcome of IVF/ICSI.

Methods: In a multicentre prospective cohort study, women entering their first cycle of IVF/ICSI treatment were asked to participate. From each participant three nocturnal urine samples were collected; pre-treatment, before ovum-pickup (OPU) and before embryo-transfer (ET) to assess hormonal concentrations. Additionally, two questionnaires were administered before the start of the treatment to measure anxiety and depression.

Result(s): 168 women completed the questionnaires and collected at least two urine specimens. A significant positive correlation between urinary adrenaline concentrations at baseline and ET and the scores on depression at baseline were found. In women with successful treatment lower concentrations of adrenaline at OPU and lower concentrations of adrenaline and noradrenaline at ET, compared with unsuccessful women, were found.

Conclusion(s): The significant positive association of adrenaline concentration with pregnancy and with depression, suggested that this adrenal hormone could be one of the links in the complex relationship between psychosocial stress and outcome after IVF/ICSI.

Introduction

In vitro fertilization (IVF)/Intra cytoplasmatic sperm injection (ICSI) is a stressful experience and its outcome may be influenced by many known and still unknown factors. In addition to biomedical factors (such as age and history of pregnancy), there is increasing evidence that psychological factors, for instance anxiety and depression, are also related to IVF/ICSI treatment outcome (Demyttenaere et al. 1998; Smeenk et al. 2001). However, there are also studies in which no relationship between the psychosocial status of women and treatment outcome has been found (Boivin and Takefman, 1995; Slade et al. 1997). This discrepancy may be explained by differences in population characteristics, study design and differences in the assessment of psychosocial factors.

In general, a distinction is made between direct and indirect effects of stress. The direct effects refer to the effects mediated by the autonomic nervous system, the (neuro) endocrine system and the immune system, whereas the indirect effects imply those health changes resulting from changes in health behaviour, for instance smoking. Modulation results in an integrated adaptive psychobiological reaction pattern to environmental challenges (Vingerhoets and Perski, 2000).

Although the effects of psychosocial stressors on the activity of the sympathetic medullar system and on the hypothalamic-pituitary adrenal axis have been studied intensively (Sanders and Bruce, 1997; Gold et al. 2003; Schommer et al. 2003; Woods et al. 1998), no clear picture emerges on the exact relationship between the different types of stressors and release of stress hormones. Moreover, several authors reported low correlation coefficients between questionnaire based and hormonal indicators of stress (Sanders and Bruce, 1997; Woods et al. 1998).

So far, several reviews on stress and female reproduction have been published (e.g. Dobson et al. 2003; Ferin 1999; Greil 1997; Magiakou et al. 1997), but little is known about the relationship between psychosocial stress and the release of adrenal hormones in relation to IVF/ICSI treatment outcome. As the treatment itself most probably influences psychosocial factors, it is extremely difficult to separate cause and effect of psychosocial factors on the outcome in IVF (Boivin and Takefman, 1995). The complex relationship is mediated by an interplay of various systems, the underlying mechanisms of the relationship remain obscure so far. Even aspects of the treatment could influence the hormonal response. For instance

Luppa et al. (1995) found an increased urinary excretion of cortisol metabolites after stimulation with an GnRH agonist.
In an earlier study we demonstrated that pre-treatment levels of anxiety and depression are significantly positively related to treatment outcome in IVF/ICSI (Smeenk et al. 2001).
We hypothesized therefore that pre-treatment levels of anxiety and depression could be reflected in higher concentrations of the stress hormones cortisol and catecholamines during treatment, which in turn could influence treatment outcome.
The aim of the present study was therefore to examine the association between the concentrations of the stress hormones during treatment and the self-reported stress in order to investigate the mechanism for the negative effect of anxiety and depression on the outcome of IVF/ICSI.

Materials and methods

Participants

Patients visiting the outpatient clinic of the department of Obstetrics and Gynaecology of the University Medical Centre Nijmegen, an academic tertiary referral centre, or visiting the Amphia hospitals in Breda, a secondary referral centre, all in the Netherlands, were invited to participate in the study. They were scheduled for the first IVF/ICSI treatment cycle between January 1999 and March 2000. Details of the program and the protocol used have been described previously (Smeenk et al. 2001).
Between day 10 and 20 of the pre-medication cycle, i.e. before the start of GnRH-analogue administration (day 21), women were asked to complete questionnaires on psychological factors. In addition, the women were asked to provide urine samples. The first urine sample was obtained before treatment, so before the start of medication, at a random convenient day between day 10 and 20 of the pre-medication cycle. This day was not necessarily the day that the questionnaires were being filled out, but in the same period. The other urine samples were taken before the time of ovum pick up (OPU) and before the embryo transfer (ET), two stressful moments during treatment, as indicated by studies from Merari et al. (1992) and Johnston et al. (1987).
Signed informed consent was obtained from all participants. This study was approved by the ethical committees of the institutions. All participants were

guaranteed confidentiality, and only the principal investigator (JS) had full access to the questionnaires, concentrations of hormones in urine and the clinical data.

Sampling

Two psychological dimensions of stress were assessed in this study: anxiety and depression. Anxiety was measured by means of the Dutch version of the State Anxiety Inventory (STAI; Spielberger et al. 1970). Depression was measured using the Dutch version of the Beck Depression Inventory (BDI; Beck and Beamesderfer, 1974). Both questionnaires have shown satisfactory reliability and validity.

For endocrine assessments three nocturnal urine samples were collected. Initially, the urine sample was collected in a 2 L polypropylene bottle containing 5 mL of 6 mol/L hydrochloric acid as preservatives of the catecholamines to prevent oxidation, later we used sodium disulfite ($Na_2S_2O_5$) and Na_2EDTA as preservatives to enable us to measure cortisol in the same samples. Therefore, in the first 100 of urine samples the concentration of cortisol could not be assessed. Consequently, the sample sizes for cortisol are smaller than for the catecholamines

Women were asked to collect all urine after midnight (0.00 hours) including the first morning sample, at three timepoints during their treatment cycle:

T1: at baseline (before commencing the IVF/ICSI treatment),
T2: on the day of OPU,
T3: on the day of ET.

In the sample adrenaline, noradrenaline and cortisol levels were measured and expressed per mmol creatinine to correct for urine sample size. Urinary creatinine concentrations were measured by a modified Jaffé method on a Hitachi 747 analyzer (Boehringer Mannhein, Germany).

Levels of adrenaline and noradrenaline were determined by fluorometric determination after high performance liquid chromatography (HPLC). In short, catecholamines were extracted and subsequently derivatized. The 2,3 diphenyl-quinoxaline derivatives of adrenaline and noradrenaline were measured (Willemsen et al. 1995). The inter-assay coefficient of variation for the noradrenalin assay amounted to 4.2% (n=21) and 5.7% (n=17) at concentrations of 160±6.7 nmol/L and 403± 22 nmol/L, respectively. For adrenaline the coefficients of variations were

5.7% (n=21) and 6.2% (n=17) at levels of 63.1 ± 3.6 nmol/L and 67.4 ± 4.2 nmol/L, respectively.
Free cortisol was measured by radioimmunoassay (RIA) after extraction with dichloromethane and subsequent paper chromatography, according to the method described earlier for cortisol measurement in plasma and saliva (Meulenberg et al. 1987). To adapt this method for urinary assessment, 3H-cortisol was added as a recovery tracer to 0.1 ml of urine, before extraction by means of dichloromethane.

Successful treatment was defined as treatment resulting in a viable pregnancy, with a positive heartbeat on transvaginal ultrasound five weeks after ET.

Statistical analysis
Data analysis was performed by means of the SPSS-program (version 11.0 for windows, SPSS inc., Chicago, USA). The Spearman correlation coefficient was used to express the association between psychological and hormonal measurements (two-tailed).The distribution free Mann-Whitney test for two independent samples was used to compare hormonal findings at the various moments during treatment between pregnant and non-pregnant women (two-tailed). The nonparametric two-way ANOVA by ranks, or Friedman test, was used to detect a trend in the hormonal response during treatment (two-tailed).

Results
Two-hundred-forty-six out of 291 participants (85%) returned the questionnaires and were willing to collect urine specimens. The remaining 45 patients did not participate because of hygienic or logistic reasons.
Only women of whom questionnaire data and at least two urine specimens (T1 and T2) were available, were included in the analysis. A dataset was obtained in 36 women (66% of the participants) coming from Breda and 132 (69%) coming from Nijmegen. The main reason for incomplete data was that a number of women forgot to collect the urine the morning before ovum pick-up. The samples of one participant were discarded from analysis since the levels of adrenaline and noradrenaline at T1 showed extreme variation (>1000%) compared with the levels at T2 and T3.
Unfortunately, the first 100 urine samples were acidified directly after obtaining the sample and therefore the concentration of cortisol could not be assessed.

Consequently, the sample size for cortisol is smaller than for the catecholamines and the sample size varies over the various stages of treatment.

Since no significant differences were found in anxiety (p=.40) and depression (p=.29) scores, and between adrenaline (p=.24), noradrenaline (p=.42) and cortisol (p=.09) concentrations in urine, between the participants of the two participating centres, the statistical analyses were based on the combined dataset of both cities, resulting in a sample of 167 women (68% of all participants).

Table I: Demographic and psychological characteristics of the participants (n=168)

Measure	Mean	SD	Range	Median
Age (years)	34.3	3.5	25-42	34
Duration of Infertility (ys)	3.7	2.1	1-13	3
State anxiety score	36.6	9.1	20-61	36
BDI score	5.4	4.7	0-27	5

Table I shows characteristics on demographic and psychological variables of the participants.

The ongoing pregnancy rate after the cycle was 32%. During treatment, 16% (n=27) of the participants did not reach embryotransfer, due to cancellation by the patient, poor response, ovarian hyperstimulation syndrome or total fertilization failure. Women who forgot to collect urine samples on T3 did not show statistically significant differences on demographic, psychological or outcome variables compared with the women did not forget to collect urine.

No statistically significant differences were found between pregnant and non-pregnant women on age (p=.12), duration of infertility (p=.73), anxiety (p=.28), depression (p=.11), but also on the number of follicles (p=.25), number of oocytes (p=.45) and number of embryos (p=.07).

Table II: Characteristics of the hormonal measures (nmol/mmol creatinin)

Measure	n	median	minimum	maximum	SD
Adrenaline T1	167	0.82	0.25	6.49	0.89
Adrenaline T2	167	0.81	0.18	5.90	0.81
Adrenaline T3	83	0.72	0.07	4.63	0.84
Noradrenaline T1	167	15.98	0.97	40.00	6.54
Noradrenaline T2	167	15.62	0.24	44.87	6.87
Noradrenaline T3	83	15.52	0.99	40.19	6.67
Cortisol T1	120	3.50	0.08	30.48	4.24
Cortisol T2	129	2.92	0.06	12.50	2.96
Cortisol T3	68	3.18	0.04	36.36	5.45

A large variation between subjects was found for each of the hormones (Table II). Table III shows the correlation between the State Anxiety Inventory and the Beck Depression Inventory scores and endocrine variables. Depression scores were positively associated with concentrations of hormones. In particular, a significant positive association was found between adrenaline pre-treatment (.17) and at the time of embryo transfer (.25) and the pre-treatment findings on depression. An association for anxiety with adrenaline was found as well, although this did not reach statistical significance.

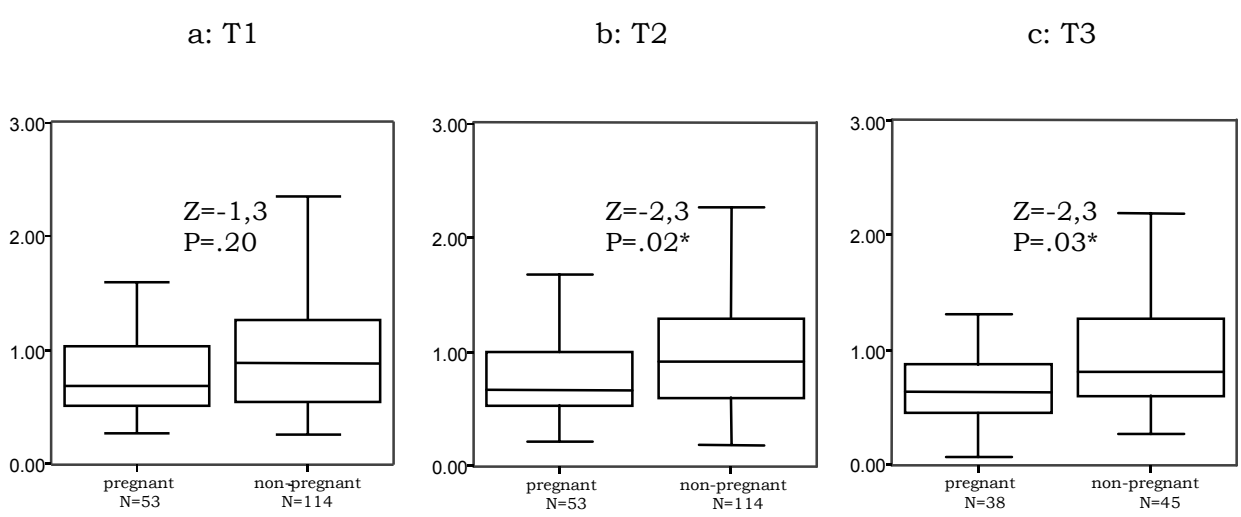
Table III: Correlations of questionnaire findings and endocrine measurements (nmol/mmol creatinin) Spearman's rho

	STAI-State	BDI score
Adrenaline T1	.12 (p=.12)	.17 (p=.04)*
Adrenaline T2	.14 (p=.08)	.14 (p=.08)
Adrenaline T3	.21 (p=.06)	.25 (p=.02)*
Noradrenaline T1	.06 (p=.56)	.09 (p=.28)
Noradrenaline T2	.03 (p=.74)	.01 (p=.86)
Noradrenaline T3	.11 (p=.34)	.16 (p=.14)
Cortisol T1	.06 (p=.52)	.13 (p=.16)
Cortisol T2	.20 (p=.02)*	.18 (p=.04)*
Cortisol T3	-.08 (p=.52)	-.10 (p=.42)

Furthermore, a significant association was found between cortisol concentrations at T2 and the pre-treatment findings on anxiety (.20) and depression (.18). Exploratively, these analyses were repeated in subgroups comparing successfully, meaning pregnant, or unsuccessfully treated women. The correlation coefficients were stable.

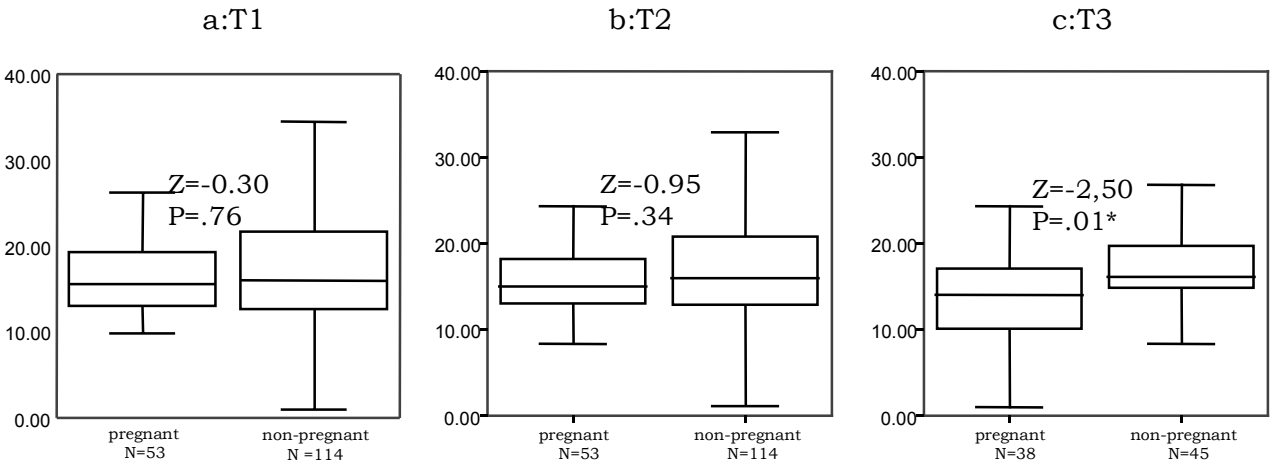
Next, hormonal levels between successfully and unsuccessfully treated women were compared. The figures show the concentrations of stress hormones during the various stages of treatment, in comparing pregnant and non pregnant women.

Figure 1: adrenaline/creatinin (nmol/mmol creatinin) during treatment, comparing pregnant and non-pregnant women



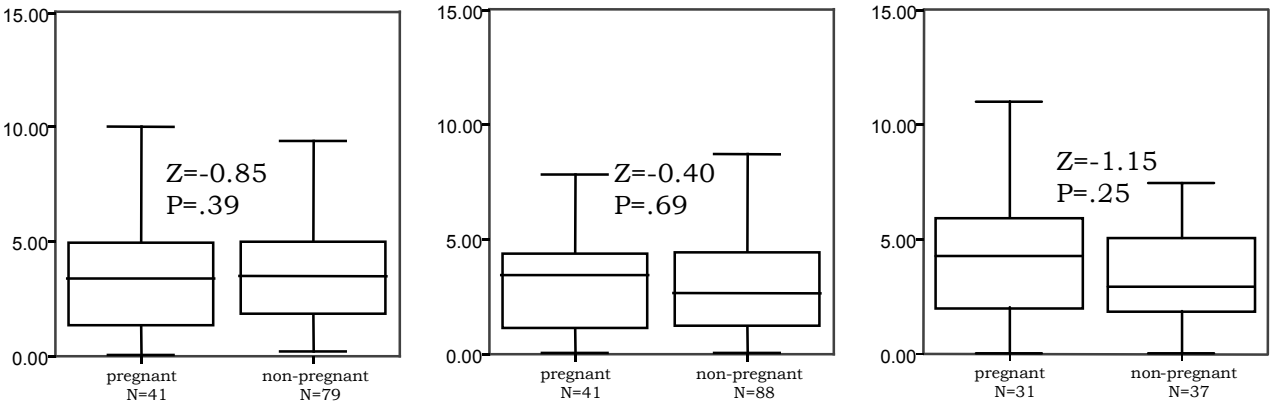
Box-and-Whisker plots were used to present the data, without displaying the outliers, which did not fit the scales of the figures. The outliers were used in the statistical analyses.

Figure 2: noradrenaline/creatinin during treatment, comparing pregnant and non-pregnant women



Significantly higher levels of adrenaline at the time of ovum pick-up (figure 1b) and embryo transfer (figure 1c) and on noradrenaline at the time of embryo transfer (figure 2c) were found in unsuccessfully versus successfully treated women. No significant hormonal differences were found pre treatment (figure 1a, 2a). In addition, no significant differences were found on cortisol (figure 3a, 3b, 3c) .

Figure 3: cortisol/creatinin during treatment, comparing pregnant and non-pregnant women



The concentration of adrenaline showed a downward trend during treatment (Chi=10.51; p=.005). In comparing the different stages of treatment, significantly lower levels of adrenaline were found at T3 in comparison with T1 (Z=-2.2; p=.03) and T2 (Z=-2.5; p=.01). No significant changes were found for the concentrations of noradrenaline (Chi=.68; p=.71) or cortisol (Chi=.56; p=.76) during treatment. No significant differences could be observed between unsuccessfully versus successfully treated women with regard to the pattern of hormonal response across treatment.

Discussion

The aim of the present study was to investigate the relationship between pre-treatment psychological findings and stress hormones during IVF/ICSI treatment. Additionally, the hormonal levels at various stages of treatment were compared between successfully and unsuccessfully treated women. Furthermore, the hormonal response during treatment was assessed.

A positive association between adrenaline levels during treatment and scores on pre-treatment depression was found. A similar, although not significant, association was found between adrenaline and pre-treatment anxiety. Cortisol levels at the time of OPU were found to be associated with pre-treatment anxiety and depression scores, whereas no associations were found for noradrenaline. The correlation coefficients between questionnaire based and hormonal indicators of stress are comparable with those reported in previous publications (Sanders and Bruce, 1997; Woods et al. 1998).

There was a considerable inter-individual variation in baseline values of the hormones in this study. In a previous study similar high variation in hormones were found and these could not be explained by menstrual cycle, behavioural, emotional or cognitive stress reactions (Hansen et al. 2001).

Overall, the concentration of adrenaline at the time of ET was found to be significantly lower than the concentrations of adrenaline at the time of OPU or at baseline. A remarkable finding in our study was that successful treatment was associated with significantly lower levels of adrenaline at the time of OPU and ET and lower levels of noradrenaline at the time of ET. The implantation phase seems to be involved, as other treatment variables were not found to differ between the outcome groups. Whether the effect of adrenaline is directly or indirectly, however,

needs further exploration. To our knowledge, no previous reports on the effect of adrenaline on treatment outcome in IVF exist.
The correlation of adrenaline concentrations with BDI was higher than with STAI. This could be due to fact that the chronic nature of the threatening infertility was of more importance than the acute state stress, related to the treatment itself. During treatment a decrease in the concentration of adrenaline was found, which could be explained by high levels of anxiety in anticipation of treatment. No decrease was found in the concentrations of the other stress hormones. This finding is in contrast with Harlow et al. (1996) who found an increase in cortisol during IVF-treatment. However, some of the differences could be explained by the methodology. As most cortisol in blood is bound to a carrier protein, whereas in urine it is unbound, assays measuring cortisol in blood and urine are not necessarily measuring the same thing.

In our study the stress response during treatment did not differ between women who became pregnant after treatment and those who did not become pregnant. This finding suggests that the response itself cannot account for the observed difference in treatment outcome. Furthermore, in this sample no differences were observed on pre-treatment psychological measures between the two outcome groups, possibly due to the smaller sample size.

Although the relationship between psychosocial stress and infertility has been studied intensively, so far little is known about the effects of catecholamines and cortisol on physiological processes involved in reproduction.
Studies encompassing both catecholamines and cortisol in this particular field are extremely rare. Cortisol was studied far more often over the years, thus resulting in more hypotheses.
Catecholamines may affect fertility by altering uterine blood flow (Schenker et al. 1992). Cortisol, having immuno-suppressant properties, may affect immunological conditions needed for implantation. Furthermore, it was found that cortisol levels in follicular fluids in stimulated cycles were correlated with oocyte maturity and in vitro fertilizability (Fateh et al. 1989). A direct effect on granulosa cells affecting steroidogenesis and an influence on oocyte quality was proposed by Michael and Cooke (1994). However, in most studies merely an association is presented, as in

our study, since optimal research is hardly possible under 'in vivo' circumstances in this field.

Recently, Lewicka et al. (2003) have shown that a higher serum cortisol/follicular cortisol ratio was associated with pregnancy. Csemiczky et al. (2000) found that infertile women have elevated stress levels in terms of circulating prolactin and cortisol levels compared to the fertile controls.

Stress was previously found to be associated with high amounts of activated T cells and reduced implantation rates in IVF-women (Gallinelli et al. 2001). Demyttenaere et al. (1992) indicated that women with high anticipatory state anxiety levels and high anticipatory cortisol concentrations have lower pregnancy rates in IVF. Facchinetti et al. (1997) demonstrated a negative correlation between stress susceptibility and outcome of IVF. Furthermore, Demyttenaere et al. (1991) suggested that personality dependent stress responses are important for conception rates in stimulated cycles. On the other hand women undergoing IVF were found to respond biophysically different to psychosocial stressors than controls (Lindheim et al. 1995).

A limitation of the study could be the possibly confounding relation between ovarian and stress-hormones. The relation between ovarian hormones and the effect on catecholamines and cortisol was only scarcely investigated so far.

Kerdelhue et al. (1997) concluded that the absence of changes in the activity of the corticotrophic axis during the hormonal stimulation of IVF suggests that there was no major stress component associated with the stimulation phase, although in this study cortisol wasn't assessed. Luppa et al. (1995) did find an increased urinary excretion of cortisol metabolites after stimulation with an GnRH agonist, but only in women with polycystic ovarian syndrome, and not in healthy premenopausal women. Hirshoren et al. (2002) found that hormonal changes during the normal menstrual cycle affect noradrenaline, although the correlations with ovarian hormones were very small.

Sanders and Bruce (1999) concluded after studying hormonal and psychological measures of stress, that menstrual cycle quality does not account for the association between conception with more favourable moods.

Ferin (1999) stated in a review on stress and the reproductive cycle that sex steroids may interact with both central and peripheral substrates of stress, thereby possibly modifying the hypothalamic-pituitary-adrenal axis.

Overall, hormonal treatment, and consequently the altered ovarian hormones, influence hormonal stress responses. The exact mechanism, however, remains unclear.

We conclude that anxiety and especially depression before IVF/ICSI treatment were positively associated with urine adrenaline levels during treatment. However, there was a large overlap in levels of this hormone between successfully and unsuccessfully treated women, which limits the applicability in daily clinical practice. A drop in adrenaline concentrations at the time of ET was found. Lower concentrations of adrenaline at the time of OPU and ET and lower levels of noradrenaline at the time of ET were found in women with successful treatment. Adrenaline, therefore, might be an important factor in the complex relationship between psychosocial stress and outcome after IVF/ICSI.

We recommend that future studies relating stress to treatment outcome, should encompass all known aspects of stress, e.g. psychological aspects, the autonomic nervous system and the (neuro) endocrine system.

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Part III

Consequences of IVF on psychological outcome

8

A longitudinal, prospective study on emotional adjustment before, during and after consecutive fertility treatment cycles

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Abstract

Background: A longitudinal study into the course of the emotional response to IVF from pre-treatment to six months post-treatment and factors that contributed to that course.

Methods: 148 IVF patients and 71 partners completed self-report questionnaires on anxiety, depression, personality characteristics, meaning of fertility problems, coping, marital relationship and social support at pre-treatment. Assessments of anxiety and depression were repeated immediately following the final treatment cycle and again six months later.

Results: Women showed an increase of both anxiety and depression after unsuccessful treatment and a decrease after successful treatment. Men showed no change in anxiety and depression neither after successful nor after successful treatment. In the six months after unsuccessful treatment, women showed no recovery. At follow-up, more than 20% of the women showed sub-clinical forms of anxiety and/or depression. Personality characteristics, meaning of the fertility problems, and social support determined the course of the emotional response.

Conclusions: Most women adjusted well to unsuccessful treatment but at follow-up, a considerable part still showed substantial emotional problems. Personality characteristics, pre treatment meaning of the fertility problems and social support have shown to determine the adjustment to unsuccessful IVF in women. This allows early identification of women at risk as well as tailored interventions.

Introduction

Fertility problems consist of both medical and emotional aspects. While the physical impact of the medical treatment is considerable (Evers and Te Velde, 1999), couples considered emotional aspects more stressful (Kopitzke et al. 1991). For most couples, unsuccessful in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) treatment means the end of further medical treatment possibilities. This does not, however, signal the end of emotional suffering. How do couples adjust emotionally to unsuccessful fertility treatment? Despite a great deal of research into the emotional aspects of IVF and ICSI treatment, there are still few longitudinal studies on emotional adjustment before, between and after different consecutive treatment cycles. These types of studies would provide insight into the course and intensity of emotional response to treatment. In addition, the study would make it possible to identify those factors that contribute to the course of emotional adjustment. This would enable couples at risk of developing severe emotional problems as a result of one or more unsuccessful treatment cycles to be identified in time and offered counselling.

The stressor of fertility problems comprises various elements: the threat of treatment and possible childlessness, uncertainty and uncontrollability of treatment outcome, and the loss of hopes of pregnancy and creating a family with one or more children (Dunkel-Schetter and Lobel, 1991). Threatening situations with much uncertainty about the course they will take can evoke anxiety. A sense of loss, and loss of control can evoke feelings of depression. Differentiating between anxiety and depression is important because they both require different psychosocial interventions (Hawton et al. 1989).

Previous cross-sectional studies on the course of emotional response to fertility problems in general have compared groups of patients in different phases of fertility treatment. These studies revealed curvilinear relationships between length of treatment and emotional adjustment in women before they started IVF or ICSI treatment with most distress in those with moderate length of treatment compared to those with less and more length of treatment (Boivin et al. 1995, Berg and Wilson, 1991). After the start of IVF or ICSI, a positive relationship between distress and the number of unsuccessful treatment cycles was found (Slade et al. 1997; Beaurepaire et al. 1994). After ceasing fertility treatment, however, negative emotional response seems to decrease as time passes, indicating that couples seem to eventually adjust to their infertility (Daniluk, 2001; Hammarberg et al. 2001;

Leiblum et al. 1998; Weaver et al. 1997). However, there is a lack of longitudinal studies that supported these findings.
A few prospective studies have been carried out to predict emotional response to fertility treatment (Terry & Hynes, 1998; Litt et al. 1992).

These studies supported the idea that optimism and acceptance of fertility problems are protective factors in adjustment to unsuccessful fertility treatment. Both studies predicted emotional response to only one treatment cycle and did not differentiate between anxiety and depression.
Next to optimism and acceptance, there are other factors that might predict emotional response to unsuccessful fertility treatment. Selection of possible predictors can be based on stress vulnerability models (e.g. Holahan et al. 1996; Ormel et al. 1991; Costa et al. 1996). Neuroticism, cognitions of helplessness when faced with a stressor, avoidant coping and dissatisfaction with the marital and sexual relationship are identified as risk factors, while optimism, acceptance of the stressor, and the perceived availability of social support are identified as protective factors for the development of emotional problems as the result of a severe stressor (see e.g. Evers et al. 2001; Alloy et al. 1999; Terry & Hynes, 1998; Costa et al. 1996; Aldwin 1994; Carver et al. 1993; Cohen and Wills, 1985).
In previous studies (Verhaak et al. 2001; Verhaak et al. 2005), we have investigated short-term emotional response to the first IVF or ICSI treatment cycle (assessments took place four weeks after the pregnancy test following the first cycle). In addition, we have investigated a comprehensive model that incorporates several important risk and protective factors in order to predict the short-term emotional response to the first unsuccessful treatment cycle. These studies revealed an increase in anxiety and depression after the first unsuccessful cycle. In addition, they supported the importance of neuroticism, cognitions of helplessness when faced with fertility problems and dissatisfaction with the marital relationship as risk factors for the development of higher levels of anxiety and depression. In addition, acceptance of fertility problems and perceived social support were indicated as protective factors for the development of higher levels of both anxiety and depression.
In the present paper, we examined long-term emotional response of women to consecutive treatment cycles and tested the validity of the comprehensive model for investigating factors that contributed to the course of the emotional response to repeatedly unsuccessful IVF or ICSI treatment cycles six months after the final

cycle. We were interested in the set of factors that account for the most explained variance in long-term changes in anxiety and depression. In addition, we explored the long-term emotional response to consecutive treatment cycles in men.

Materials and methods

Participants

Participants were recruited at a university hospital in a medium-sized city in the Netherlands. Inclusion criteria: Dutch-speaking and about to start their first cycle of a new IVF or ICSI treatment.

Three hundred and seventy-five women and 340 of their partners agreed to participate. Two hundred and eighty-eight women responded to questionnaires after the first treatment cycle (77%). After the last cycle, 205 of these 288 women (71%) completed all the questionnaires and 147 of these 205 women (72%) also took part in the follow-up assessments. Two hundred and twenty-two of 340 men responded after the first treatment cycle (65%). After the last treatment cycle, 125 of these 222 (56%) responded and 71 of these 125 also took part in follow-up assessments (57%). Complete data sets for three measurement points were received from 148 women (40%) and 71 of their partners (21%). Demographic characteristics for these women and their partners are presented in Table 1.

The course of the emotional response was investigated for women and men after both unsuccessful and successful treatment. Factors that contributed to the course of the emotional response were only investigated in women after unsuccessful treatment.

Differences in response between women and men were due to a last recall procedure that focussed on women only.

Table 1: Participants' demographic characteristics (women= 148; men= 71)

Cause of fertility problems	
Women	23%
Men	40%
Both	8%
Idiopathic	29%
Already having children	20%
Duration of fertility problems <3 ys	26%
Between 3 and 5 years	54%
More than 5 years	20%
Mean age of women	34.1 (range: 21-43)
Mean age of men	36.3 (range: 26-54)

Design

Data was collected before the start of medication, i.e. five to ten days before the start of the first IVF/ICSI treatment cycle, four weeks after the pregnancy test subsequent to this and possible next treatment cycles, and six months after the last cycle.

For the present study, data was used from pre-treatment assessments (T1), assessments made just after the final cycle (T2) and follow-up assessments (T3). To obtain information about how women coped with the unsuccessful treatment cycle 4 weeks after the pregnancy test following the first cycle, the women were asked to complete a coping questionnaire focusing on that treatment cycle.

A cycle was retrospectively defined as a 'final' cycle when couples did not start further treatment within one year subsequent to the previous cycle. Exclusive criteria for the last treatment cycle are unobtainable, as women may again consider participation in treatment options even years after ceasing treatment (Van Balen

and Trimbos-Kemper,1995; Leiblum et al. 1987). Psychological and clinical parameters were assessed at T1, before the start of the first treatment cycle.
Anxiety and depression assessments were repeated at T2 and T3.

Procedure

Women and their partners were asked to participate in the study when at the hospital for an intake interview with their physician prior to their first IVF or ICSI treatment cycle. A long protocol (three weeks) was used. After obtaining written informed consent, questionnaires were sent to their homes. Women and their spouses were asked to complete the questionnaires separately before the start of medication and return them to the hospital in a prepaid envelop. In addition, participants received a questionnaire four to six weeks after the pregnancy test for each cycle. A final questionnaire followed six months after the last treatment cycle. If a new cycle was started within six months after this time (twelve months after the last cycle), this questionnaire was not taken into account. The study was approved by the hospital ethical research committee.

Measures

Demographic (age, educational level, number of children) and gynaecological (duration of fertility problems) background characteristics were assessed with a self-report questionnaire.
State anxiety and depression were assessed with two standardised questionnaires, validated for the Dutch population. State anxiety was measured with the 'State and Trait Anxiety Inventory' (STAI; Spielberger et al. 1983; Dutch translation: Van der Ploeg et al. 2000; 20 items, possible range 20-80). Cronbach's alpha was .90 for state anxiety. The score of one standard deviation above the mean for the norm group was used as the cut-off for clinically relevant forms of anxiety. This was 48.
Depression was measured with the 'Beck Depression Index – PC' (BDI: Beck et al. 1997; 7 items, possible range 0-28). Cronbach's alpha was .84. This is a short version of the BDI, consisting of items referring only to cognitive aspects of depression.
This makes it possible to assess depression in a medical population without confounding between medical problem characteristics and vital aspects of depression (Verhaak et al. 2001). The cut-off score for subclinical relevant forms of depression was 4 (Beck et al. 1997).

Two personality factors were measured, neuroticism and optimism. Neuroticism was measured with one subscale of the Dutch version of the 'Eysenck Personality Questionnaire' (Sanderman et al. 1995; 6 items). The possible range of the scale was 0 to 12. Cronbach's alpha in the present study was .81. Optimism was assessed with the optimism scale of the 'Life Orientation Test' (LOT: 12 items, possible range 0-32), developed by Scheier and Carver (1985) and translated into a Dutch version by Vinck et al. (1998). Cronbach's alpha in the present sample was .81.

Infertility-related cognitions of helplessness and acceptance were measured with the 'Illness Cognitions Questionnaire' (Evers et al. 2001), which was adjusted to the situation of women facing fertility problems. The possible range of both the helplessness and acceptance scales, each consisting of six items, was 6 – 24. An example of a helplessness item is: 'I felt overwhelmed by my fertility problems'. An example of the acceptance scale is: 'I can handle the problems related to my infertility.' In the present study, Cronbach's alpha was .86 for the helplessness scale and .89 for the acceptance scale.

Coping was assessed with the 'Cope' (Carver et al. 1989; 39 items). The Cope factors were clustered in four groups, resembling factors used by Terry and Hynes (1998) in their study on coping with infertility: Problem Management (Cope factors 'active coping' and 'planning'; Cronbach's alpha = .76), problem appraisal ('behavioural disengagement' and 'positive reinterpretation'; Cronbach's alpha = .58), emotional approach ('seeking instrumental support,' 'seeking emotional support,' and 'venting emotions'; Cronbach's alpha=.86), and cognitive avoidance or escapism (Cope factor 'denial'; Cronbach's alpha = .75). The reliability of the problem appraisal scale was too limited and we did not use it in our analyses.

The assessed indicators of social support were satisfaction with the marital and sexual relationship as well as general aspects of social support. Marital and sexual satisfaction was measured with the general marital satisfaction scale (10 items, possible range 0-80) and the sexual satisfaction scale (5 items, possible range 0-40) from the 'Maudsley Marital Questionnaire' (MMQ: Arrindell et al. 1983). Higher scores are an indication of greater dissatisfaction. Cronbach's alpha in the present study was .85 for general marital satisfaction and .70 for sexual satisfaction.

General aspects of social support were measured with a Dutch self-report questionnaire 'Inventory for Social Support' (Van Dam-Baggen and Kraaimaat, 1992), which measures the size of the social network (in terms of the number of friends and acquaintances) and perceived social support (20 items, possible range 5-20). In the present study, Cronbach's alpha was .87 for perceived social support.
Demographic aspects, anxiety, depression, and marital satisfaction were assessed in both women and men, the other variables were assessed in women only.

Statistical analyses

MANOVAs with repeated measures and post hoc ONEWAY analyses of variance were performed to examine differences in the course of anxiety and depression between pregnant and non-pregnant participants. Analyses were carried out separately for women and men, because of the discrepancy in participation between men and women. MANOVAs for repeated measures were performed separately after successful and unsuccessful treatment to analyse possible differences in the course of anxiety and depression with respect to the number of treatment cycles and having children.
McNemar's nonparametric test for repeated samples was used to investigate differences in the proportion of subclinical forms of anxiety and depression between different measurement points.
Pearson's correlation coefficients (in the event of nominal variables, Kendall's rank correlation coefficient was used) were calculated between the vulnerability factors and anxiety and depression change scores to explore the relationship between background characteristics and vulnerability factors assessed prior to treatment and changes in emotional status between pre-treatment (T1) and follow-up (T3) assessments. Residual gain scores were used as change scores (Kerlinger, 1975). Residual gain scores are chance scores in which the influences of pre-test scores are removed. They were calculated by regressing T3 scores onto T1 scores, creating a new variable: Time 3 with the effect of Time 1 removed. The regression analyses were sequentially performed for anxiety and depression at T3, as dependent variables. Levels of anxiety and depression at T1 were entered as first predictors. Personality characteristics are relatively stable and have been shown to determine characteristics like cognitions, coping and social support (Clark et al. 1994). For that reason, we entered them in the second step. In the third step, the additional predictors that significantly correlated with change scores in anxiety or depression

were entered This procedure provided an opportunity to examine the additional predictive value of cognitions, coping and social support, in addition to pre-treatment anxiety and depression and to relatively stable personality characteristics.

Results

T-tests did not reveal any pre-treatment differences in anxiety (t(1,147)= -.21; p=.83), depression (t(1,147)= .48; p=.63), marital dissatisfaction (t(1,147)= .50; p=.62) or sexual dissatisfaction (t(1,147)= .74; p=.46) between women whose spouses did or did not participate in the study at all or dropped out during the study.

However, six months after the last treatment cycle, women whose spouses did not participate showed higher levels of depression (t(1,147)= 3.17; p=.002) and a trend of higher levels of anxiety (t(1,147)= 1.79; p=.08) than women whose spouses did participate in the study.

In addition, t-tests did not reveal any significant difference in pre-treatment anxiety (t(1,375)= -.20; p=.84) and depression (t(1,375)= -.29; p=.78) between women who completed all questionnaires and women who did not. This was the same for anxiety (t(1,205)= -.68; p=.50) and depression (t(1,205)= -.13; p=.91) just after the last treatment cycle.

Eighty-three women (56 %; with 54 partners included in the study) got pregnant after one or more treatment cycles, 66% of these 83 after one cycle, 25% after two cycles, 6% after three cycles and 3% after four or more cycles. The other 65 (44%; with 17 partners included in the study) did not get pregnant; 27% of these 65 completed one treatment cycle, 26 % two cycles, 35% three cycles and 12% four or more cycles. The average time between T1 and T2 was three months (range 2 – 4). The average time between T1 and T3 was 16 months (range 8 – 36).

Course of anxiety and depression

The descriptive results of anxiety and depression levels at the various assessment points are presented in Table 2. The correlation between anxiety and depression was .62 at T1, .73 at T2 and .76 at T3.

MANOVAs for repeated measures were performed in order to investigate the differences in the course of anxiety and depression between T1, T2 and T3 for women and men after successful and after unsuccessful treatment.

Table II: Mean scores for state anxiety and depression in women after successful (n = 83) and unsuccessful (n=65) treatment and in men after successful (n=54) and after unsuccessful (n=17) treatment at T1 (pre-treatment), T2 (after the final treatment cycle) and T3 (six months after the final treatment cycle).

	pregnant women	non-pregnant women	men with pregnant women	men with non-pregnant women
State anxiety T1	36.7 (10.1)	37.3 (11.7)	32.8 (6.8)	33.5 (11.7)
State anxiety T2	33.5 (8.7)	40.2 (11.8)	32.3 (6.9)	34.9 (10.2)
State anxiety T3	34.2 (8.5)	39.0 (13.6)	32.3 (8.6)	32.4 (8.0)
Depression T1	1.5 (1.8)	1.5 (2.3)	0.7 (0.9)	1.0 (1.3)
Depression T2	0.8 (1.3)	2.3 (2.7)	0.6 (0.9)	1.5 (2.2)
Depression T3	0.5 (0.9)	2.3 (2.9)	0.4 (1.1)	0.8 (1.0)

The results of the MANOVAs for women did not reveal any significant effect for time for either anxiety or depression. However, a significant interaction effect for time x treatment outcome was indicated for anxiety ($F(2,146)= 6.5$; $p=.00$) and for depression ($F(2,146)= 12.9$; $p=.00$). In addition, there were significant effects for treatment outcome for both anxiety ($F(2,146)= 7.5$; $p=.01$) and depression ($F(2,146)= 16.1$; $p=.00$). Post hoc t-tests for non-pregnant women revealed a significant increase in both anxiety ($t(1,64)= -2.5$; $p =.02$) and depression ($t(1,64)= -2.9$; $p=.01$) between T1 and T2, while pregnant women showed a decrease in anxiety ($t(1,82)= 3.2$; $p=.00$) and depression ($t(1,82)= 3.4$; $p=.00$) in the same period. Post hoc t-tests did not reveal any change in anxiety ($t(1,64)= -.74$; $p=.46$) or depression ($t(1,64)= .18$; $p=.86$) between T2 and T3 in both pregnant and non-pregnant women.

The results of the MANOVAs for men did not reveal any significant time, interaction or treatment outcome effects for anxiety or any interaction and outcome effects for depression. They did reveal, however, a significant time effect for depression ($F(2,69)= 5.1$; $p=.01$). Post hoc t-tests for men after successful treatment revealed a significant decrease in depression ($t(1,53)= 2.7$; $p=.01$) between T2 and T3. The post hoc t-tests did not reveal any other significant results.

Differences in the course of anxiety and depression with respect to number of treatment cycles and already having children

Additional MANOVAs were performed for women who did not get pregnant in order to investigate possible differences in the course of anxiety and depression with respect to the number of unsuccessful treatment cycles undergone.

These MANOVAs did not show any differences in the course of anxiety and depression between women who ceased treatment after two or less cycles versus three or more (interaction effect time x number of cycles: $F(2,63)= 1.06$; $p=.35$ for anxiety and $F(2,63)= .24$; $p=.78$ for depression; time effect: $F(2,63)= .02$; $p=.83$ for anxiety and $F(2,63)= 1.19$; $p=.28$ for depression). In addition, MANOVAs performed in order to investigate differences in the course of anxiety and depression between women with and without children did not reveal any significant difference in the course of anxiety (time x children $F(2,63)= .18$; $p=.83$; children $F(2,63)= .00$; $p=.96$) or depression (time x children $F(2,63)=1.13$; $p=.33$; children $F(2,63)= .00$; $p=.99$). MANOVA's for men were not performed because of insufficient sample size (N=17).

Subclinical forms of anxiety and depression

At T1, before the start of the first treatment cycle, 13% of the women in the unsuccessful group scored above the cut-off scores for subclinically relevant forms of anxiety. This was 23% at T2 and 20% at T3. Six percent showed subclinical levels of anxiety at T2 as well as at T3. With respect to subclinical forms of depression at T1, 12% of the women who did not get pregnant scored above the cut-off. This was 20% at T2 and 25% at T3. This was a significant increase from T1 to T3 (McNemar: $p=.04$). Again, 6% showed subclinical levels of depression anxiety at T2 as well as at T3. At all measurement points, the percentage of men of both pregnant and non-pregnant wives who scored above the cut-off for clinically relevant forms of anxiety and depression varied from 0 to 2 percent.

Factors that contributed to the course of anxiety and depression after unsuccessful treatment. In Table 3, correlations of change scores for anxiety and depression between T1 and T3 with background variables and predictors are presented.

Table III: Pearson correlation coefficients between predictors and change scores for anxiety and depression between T1 and T3

	Total course (T1 – T3)	
	Anxiety	Depression
Demographic		
- Age	.08	.15
Clinical		
- Duration of infertility	-.20	-.17
Personality characteristics		
Neuroticism	.31*	.47**
Optimism	-.22	-.34**
Infertility-related cognitions		
Helplessness	.10	.32*
Acceptance	-.17	-.31**
Coping		
Problem management	.06	-.01
Emotion Approach	.22	.11
- Cognitive avoidance	.08	-.15
Social support		
General marital dissatisfaction	.30*	.28*
Sexual dissatisfaction	.15	.23
- Perceived social support	-.37**	-.34**

** p < .01; *p < .05

In predicting the change in anxiety from T1 to T3, factors which correlated significantly with the change score of anxiety were selected for the regression model: neuroticism, general marital dissatisfaction and perceived social support. Correlations between the different predictors are presented in Table 4.

Table IV: Intercorrelations for predictor variables

	1	2	3	4	5	6	7
1. Neuroticism	--	-.35**	.31*	-.34**	.46**	.21	-.41**
2. Optimism		--	-.14	.11	-.39**	-.08	.06
3. Helplessness			--	-.60**	.13	.12	-.19
4. Acceptance				--	-.09	-.27*	.30*
5. Marital dissatisfaction					--	.30*	-.38**
6. Sexual dissatisfaction						--	-.20
7. Perceived social support							--

** p<.01; * p< .05

The results revealed that T1 levels of anxiety (delta R^2= .27; p<.001), neuroticism (delta R^2 = .08; p<.01) and perceived social support, together with general marital dissatisfaction (delta R^2= .07; p<.05) added significant additional variance in anxiety levels at T3. The model with these factors fully explained 42% of the variance in anxiety at T3 (R^2= .42; p<.05).

In predicting depressed mood at T3, the six factors that correlated significantly with the change score were taken into account and entered in the regression analysis: baseline levels of depression in the first step, personality characteristics neuroticism and optimism in the second step, cognitions of infertility (helplessness and acceptance) in the third step and social support (general marital dissatisfaction and perceived social support) in the last step. The results revealed that baseline levels of depression (delta R^2= .09; p<.05), and personality characteristics (delta R^2= .22; p<.001) added significant additional variance in depression levels at T3. The model that explained the most variance (R^2= .36; p<.000) consisted of baseline levels of depression, neuroticism, optimism, helplessness, acceptance, perceived social support and general marital dissatisfaction. However, cognitive and social support factors did not significantly explain additional variance.

Discussion

One apparent result of the present study is the lack of emotional recovery in the six months after the end of treatment. Following theories on cognitive adaptation (Folkman, 1984; Taylor, 1983), one might expect a decrease in distress after abandoning treatment. This lack of recovery in the present study might be explained by the length of recovery period that was taken into account. Six months could be too short to identify beneficial effects of changing the meaning of infertility (Bananno & Kaltman, 2001). Another explanation might be found in the continuation of uncertainty about the definitive character of the childlessness which is in line with studies indicating that couples still keep new treatment possibilities in the back of their mind for a considerable time after the end of treatment (Van Balen et al. 1993; Leiblum et al. 1987).This seems to interfere with the cognitive adaptation, necessary to adjust to definitive childlessness (Folkman, 1984; Taylor, 1983).

The next apparent finding is the importance of wide range of factors that determined the emotional adjustment to infertility. Personality characteristics, cognitive factors, and social support were found to be important in this process. By investigating the predictive power of these factors in a stress vulnerability model, their relative importance could be noticed. The importance of neuroticism is in line with theories and empirical evidence regarding the interrelationship between anxiety and depression to neuroticism. Both emotions share the central aspect of negative affectivity or neuroticism (Clark et al. 1994).

The present study also supported the importance of social support as a buffer in the relationship between the stressor of unsuccessful treatment and emotional response. With respect to fertility problems, the spouse seems to be the most important source of social support (Laffont et al. 1994).

After controlling for personality characteristics and social support, cognitions of acceptance helplessness determined the course of depression. The importance of cognitive adaptation in terms of changing meaning in the adjustment to unsuccessful IVF is expressed in higher levels of acceptance as assessed in the present study and related to a more favourable adjustment to unsuccessful treatment. A lack of adaptation in terms of the inability to regain control, as assessed in higher levels of helplessness, is related to poorer outcome. Women have to make a shift from active, treatment focused ways to deal with the fertility problems to cognitive ways of adjustment in terms of changing the meaning of

childlessness. This is in accordance to theories stressing the importance of changing meaning in long term adjustment to severe health problems (Folkman, 2001; Folkman, 1984; Taylor, 1983; Rothbaum et al. 1982). The importance of personality characteristics, meaning of infertility and social support as predictors of the emotional adjustment to unsuccessful IVF is in line with the results of a previous study into the adjustment to one unsuccessful treatment cycle on the present sample (Verhaak et al. 2005).

In the present study, coping factors did not determine the adjustment to unsuccessful treatment. The effectiveness of coping partly depends on the characteristics of the stressor (Suls and Fletcher, 1985; Penley et al. 2002). The infertility stressor is highly uncontrollable (Miller-Campbell et al. 1991). Accordingly, ways to actively change the stressor are limited. That is why active and problem-focused coping are assumed to be ineffective. The results of the present study partly support this: there was no relationship found between problem-focused, active coping and changes in anxiety or depression. Some studies found support for effective coping being related to what they called emotional approach coping in the event of uncontrollable stressors: minimizing the threatening evaluation of the stressor and accepting its occurrence (Austenfeld and Stanton, 2004; Berghuis and Stanton, 2002; Terry and Hynes, 1999). The negative relationship between cognitions of acceptance of fertility problems and increase in depression between T1 and T3 in the present study is in line with these results. Findings from the present study did not support the expected positive relationship between avoidant coping and anxiety or depression. This might partly be due to the complexity of the stressor, the time lag between coping assessment and emotional response and the general way coping was assessed. Effective coping depends on the characteristics of the stressor. The stressor in the present study is complex: it is the stressor of the treatment itself, of uncertainty and of a loss of hope for pregnancy and children.

All these aspects might require different coping strategies: Avoidant coping seems to be efficacious during times of uncertainty (Miller and Mangan, 1983) Re-evaluation of the stressor seems to be important in the event of loss (Davis and Nolen Hoeksema, 2001). It is possible that a stronger coping effect might have been found if coping efforts related to these aspects of the stressor were separately assessed In addition, the effectiveness of avoidant coping seems to depend on the time lag

between the stressor and emotional response: avoidant coping seems to be more effective in the short term (Suls and Fletcher, 1985). It is possible that avoidant coping could determine short-term emotional response to unsuccessful treatment .

The long period over which assessments took place is a strength of the present study. Nevertheless, prolongation of this period to two years after the final treatment cycle would provide more information about the course of emotional adjustment to successful and unsuccessful treatment. This would be particularly interesting for the group of women who only recently (at follow-up) showed clinically relevant forms of anxiety or depression. Previous studies show equivocal results about the course of adjustment to a severe stressor. Some previous studies have indicated that high levels of depression shortly after incidence of the stressor are important risk factors for the development of a major depressive disorder in the near future (Howarth et al. 1994). Other studies, however, have indicated that the adjustment process normally takes two years, after which most people seem able to adequately adjust (Bonanno and Kaltman, 2001; Janssen et al. 1997).

A difficult aspect of the study was definition of the final treatment cycle. It hardly seems possible to investigate emotional response to definite infertility. There are couples who take a long break between cycles. Other couples hesitate for a long time before making another attempt. Previous studies have pointed out that half of the women who have stopped fertility treatment would restart if there were new treatment possibilities (Van Balen and Trimbos-Kemper 1995; Leiblum et al. 1987). It seems as if the hope of ever conceiving a child only diminishes with age. And even this criterion could perhaps change in the near future.

The high percentage of women that display subclinical forms of anxiety and depression even six months after the final treatment cycle is clinically important. The present study provided information for identifying these women before the start of the treatment, which will make it possible to offer these risk groups additional counselling in time. The counselling should be focused on the meaning or the cognitions of fertility problems and on improving social support. Future studies will have show whether these counselling efforts prevent the development of severe emotional problems.

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9

Long term psychological adjustment to in vitro fertilization/intra-cytoplasmatic sperm injection treatment in women

Human Reproduction, in press

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Abstract

Background: The aim of the present study was to gain more insight into long-term psychological adjustment to IVF in women.

Methods: In a prospective cohort study, 298 women entering their first IVF treatment cycle (including ICSI) completed standardized psychological questionnaires before the start of the treatment, just after the last treatment cycle, and six months and three to five years after the last treatment cycle. The main outcome measures were state anxiety, depression and mode of adaptation to unsuccessful IVF.

Results: anxiety and depression were found at follow-up to return to baseline levels following treatment not resulting in a live birth after an initial increase during treatment. On the other hand, treatment resulting in a live birth was found to lead to a more positive long-term emotional status. Women who focused on new life goals as a mode of adaptation three to five years after IVF without a live birth showed lower levels of anxiety and depression compared to those who persisted in their attempts to get pregnant.

Conclusions: treatment that resulted in a live birth led to more positive emotional adjustment. In addition, a majority of the women who did not give birth to a child after treatment adjusted well psychologically. Positive adjustment was related to developing new life goals rather than persisting in attempts to get pregnant. Helping women to change life goals after abandoning treatment might have beneficial effects on the adaptation process.

Introduction

IVF treatment is physically and emotionally stressful. The unfulfilled desire to have a child, and the consequent threat of permanent infertility were related to increased levels of anxiety and depression during IVF treatment (Verhaak et al. 2001). Numerous studies have been published on psychological aspects of IVF treatment. Until now, however, the long-term psychological consequences of IVFhave rarely been investigated. An earlier study found that six months after the last unsuccessful treatment more than 20% of the women showed clinical forms of anxiety and/or depression (Verhaak et al. 2005). It is known that a high level of depression shortly after the incidence of a stressor is a major risk factor for the development of a depressive disorder in the near future (Howarth et al. 1994).

On the other hand, cross-sectional studies have indicated that, in general, couples seem to adjust to their infertility (Hammarberg et al. 2001, Leiblum et al. 1998, Weaver et al. 1997; Freeman et al. 1987). A retrospective study indicated that the longer the time passed since the last IVF treatment cycle, the better the emotional adjustment (Baram et al. 1988). This is in line with the finding that the adjustment process normally takes about two years, after which most people seem able to adjust well (Bonanno & Kaltman 2001; Janssen et al. 1997).

Positive adjustment to infertility was shown to be related to abandoning medical treatment and focusing on new life goals, whereas pursuing pregnancy was related to more negative adjustment (Van Balen & Trimbos-Kemper 1994). This is in agreement with the longitudinal, qualitative study by Daniluk (2001) into emotional adjustment after unsuccessful fertility treatment, which indicated that 'turning towards the future' is an important aspect.

Since longitudinal studies on the course of the emotional response before, during and several years after unsuccessful treatment are non-existent, the question remains what happens to those women who did not succeed in getting pregnant. A longitudinal follow-up study could provide us with information about the number of patients developing clinical forms of anxiety and/or depression after treatment. Furthermore, it could provide insights into subsequent modes of adaptation. The aim of the present study was therefore to gain a greater insight into the longitudinal adjustment of women in IVF. This could provide us with more information about the desirability of tailored support after IVF is abandoned.

Materials and methods

Sample

The data used were from women who came for the first cycle of a new IVF treatment (including 38% who underwent ICSI) at the Radboud University Nijmegen Medical Center in the Netherlands between 1998 and 2000. This group participated in a previous prospective follow-up study on the psychological aspects of IVF treatment. Of the 450 women contacted, 380 (84%) agreed to participate at the start of the previous study (T1). Participants were asked to complete questionnaires on psychological factors before the start of treatment (T1), after the last treatment cycle (T2), and six months after the last cycle (T3). Last treatment cycle was defined as not starting a new cycle, one year after the end of the previous cycle. Three to five years after T1, the 380 women who completed the T1 assessment were again invited to participate in a long-term follow-up assessment (T4).

All participants were guaranteed confidentiality and a separation of the questionnaire information on psychological, marital and sexual factors and their clinical management. Written informed consent was obtained from all participants.

Psychological measures

State anxiety was measured by means of the Dutch version of the State and Trait Anxiety Inventory (Spielberger et al. 1970), a scale that shows satisfactory reliability and validity. The inventory has 20 items that assess state anxiety; the score for each item ranges from 1 to 4, with higher scores indicating greater state anxiety. Total scores therefore range from 20 to 80. The cut-off for clinical state anxiety was 48, which is one standard deviation above the mean for the age-matched norm group of Dutch women (Van der Ploeg et al. 2000).

Depression was measured by means of the short Dutch version of the Beck Depression Inventory (BDI) (Beck et al. 1997). This scale is one of the most widely used, reliable and valid instruments for assessing intensity of depression and for detecting depression in the general population. The scores for each item range from 0 (low) to 3 (high). The cut-off for clinical depression was a total score of 4.

Furthermore, four modes of adaptation were distinguished (according to Van Balen & Trimbos-Kemper 1994):

1 medical mode: still pursuing medical options in order to have a biological child of their own;
2 passive mode: not actively pursuing the desire, but still having the desire for a child;
3 alternative mode: pursuing other ways of having a child (e.g. adoption);
4 new goals: abandoning the desire to have a child and choosing other life goals.

Statistical analysis

Comparisons were made between women who gave birth to a child after the start of their IVF treatment (spontaneous pregnancies after the start of treatment were also taken into account) and women who did not. All statistical analyses were performed using the SPSS program (SPSS version 12.0). The course of anxiety and depression over time and differences in that course between women who gave birth to a child after their treatment and those who did not was examined using multivariate analysis of variance (MANOVA). Post-hoc, one-way analyses of variance were performed to examine the course of anxiety and depression in women who gave birth to a child after their treatment and those who did not. T-tests were used to compare women who gave birth and those who did not after treatment and to compare anxiety and depression at different times. One-way ANOVAs were used to compare anxiety and depression in women with different modes of adaptation.
This study was approved by the institution's ethical committee.

Results

Of the 380 women who participated in the previous study, 298 (78% of the participants) completed an additional set of questionnaires three to five years after treatment (T4). Sixty-four women (21%) already had a child before the start of the treatment. One hundred and ninety-three women (65%) gave birth to a child after IVF, 105 women (35%) did not. A non-participation study (n=82 of 380) showed a trend towards more non-responders (women who did not respond to T4) among women who did not succeed in giving birth to a child after treatment (chi=3.37; p=.07).

The mean age of the women was 33.4 years (SD=4.1). Thirty-one per cent completed ten years of education or less, 39% completed 11 to 14 years of education and 30% completed 15 years of education or more. All the women were part of a heterosexual couple at the start of the treatment, 96% was born in the Netherlands and 98% was Dutch. The causes of the fertility problems were as follows: female factor in 17% of the women, 39% male factor, 8% both male and female factors and 28% unknown.

After abandoning their treatment in the hospital where the study was carried out, seven per cent (n=22) of the respondents went for treatment elsewhere; eight of them (36%) subsequently gave birth to a child. The options indicated were: intra-uterine insemination with donor semen (n=4), intra-uterine insemination with own semen (n=1), IVF at another clinic (n=10), homeopathic medicine (n=1), other medication (n=1), and alternative medicine (n=5), which included acupuncture, magnetism and ayurvedic therapy.

The course of anxiety and depression over time was studied using MANOVAs, comparing women who did and did not give birth after treatment. When only the pre-treatment data (T1) and data from three to five years after treatment (T4) were considered, a significant interaction effect was found for time and birth, both for anxiety (F=3.9; p=.05) and depression (F=12.2; p<.01).

Table I: Anxiety and depression at pre-treatment (T1) and follow-up (T4) in women who gave birth after IVF (n=193) and those who did not (n=105)

	Pre-treatment (SD)	Follow-up (SD)	Univariate test
Anxiety[1]			
Gave birth after IVF	36.1 (8.9)	34.2 (7.6)	t=2.6; p=.01
Did not give birth after IVF	37.7 (12.2)	37.7 (10.6)	not significant
Depression[2]			
Gave birth after IVF	(1.5)	0.5 (1.3)	t=5.0; p<.01
Did not give birth after IVF	1.3 (1.9)	1.5 (2.2)	not significant

[1]significant interaction effect time x birth: F=3.9; p=.05

[2]significant interaction effect time x birth F=12.2; p<.01

In further analyzing the effect, a significant decrease in anxiety (t=2.6; p=.01) and depression (t=5.0; p<.01) was found in women who gave birth to a child. The scores for anxiety and depression for women who did not give birth to a child did not differ significantly between pre-treatment and three to five years after treatment.

A complete dataset was obtained for 107 women (T1,T2,T3,T4); 68 women gave birth to a child after treatment and 39 women did not. The smaller sample size was due to incomplete data at T2 and T3. Comparisons of anxiety and depression at T1 and T4 did not reveal significant differences between responders and non responders at T2 and T3. The same was true for pregnancy rates.

Table II: Anxiety and depression at different times during and after IVF (N=107; 68 live birth after IVF, 39 no live birth after IVF)

	T1: Pre-treatment (SD)	T2: Just after treatment (SD)	T3: 6 months after treatment (SD)	T4: 3-5 years after treatment (SD)
Anxiety[1]				
- Gave birth after IVF	36.2 (9.6)	32.8 (8.2)[3]	34.0 (8.4)	33.9 (7.5)
- Did not give birth after IVF	36.9 (13.1)	39.8 (14.5)	40.3 (15.5)	37.1 (11.1)
Depression[2]				
- Gave birth after IVF	1.2 (1.5)	0.7 (1.0) [4]	0.5 (0.9)	0.5 (1.5) [5]
- Did not give birth after IVF	1.3 (3.9)	3.9 (3.4)[6]	2.6 (2.9)	1.7 (2.2)

[1] Significant interaction effect time x birth: F=3.5; p=.02

[2] Significant time effect: F=3.2; p=.02; significant interaction effect time x birth: 4.5; p<.01

[3] Significant decrease T1-T2: t=3.1; p=.03

[4] Significant decrease T1-T2: t=2.6; p=.01

[5] Significant decrease T1-T4: t=3.0; p<.01

[6] Significant increase T1-T2: t=2.1; p=.05

The data are shown in Table 2. In analyzing the data, a significant effect over time was found for depression (F=3.2; p=.02). No significant main effect for anxiety was found. Furthermore, a significant interaction effect on time x birth was revealed for both anxiety (F=3.5; p=.02) and depression (F=4.5; p<.01). More specifically, in this particular subgroup a significant decrease in anxiety was found in women who gave birth when comparing T1 and T2 (t=3.1; p=.03), and significantly lower levels of depression were found when comparing T1 and T2 (t=2.6; p=.01) and T1 and T4 (t=3.0; p=<.01). In analyzing the women who did not give birth after treatment, higher levels of depression were found at T2 compared to T1 (t=2.1; p= .05).
When only the percentages of the group with clinically relevant forms of depression were considered, at pre-treatment (T1) 12% scored above the cut-off level; just after the last treatment cycle (T2) 20%; six months later (T3) 25%; and three to five years later (T4) 16%. When clinically relevant forms of anxiety were considered, the percentages were 13% at T1, 23% at T2, 20% at T3 and 15% at T4.

Ninety of the 105 women (86%) who did not give birth provided information about their mode of adaptation. The following modes of adaptation were indicated:
medical mode 12% (n=11), alternative mode 13% (n=12), passive mode 38% (n=34), and new goals 37% (n=33). The mean anxiety and depression scores are shown in Table 3.

Table III: Anxiety and depression according to mode of adaptation at follow-up after treatment not resulting in live birth (N=90)

Mode of adaptation	N	Anxiety	Depression
Still pursuing pregnancy wish			
- Persisting with treatment	11	44.2	3.8
- Still longing for a child	34	42.7	2.1
New life goals			
- New goals	33	32.1	1.5
- Adoption	12	34.8	0.4

Significant differences in anxiety (F=10.1; p<.01) and depression (F=9.1; p<.01) were found between the different groups. Significantly higher levels of anxiety and depression (anxiety: t=4.53, p<.01; depression: t=4.51, p<.01) were found in the two groups still pursuing a desire for pregnancy (medical and passive mode), compared to the two groups of women who had abandoned their active pursuit of pregnancy (new life goals and alternative mode). These differences were the same when women who already had a child before treatment were left out of the analyses (data not shown).

At T4,19% (n=20) of the women who did not succeed in getting pregnant already had a child before the start of the treatment. A comparison of anxiety and depression at follow-up (T4) between these women and the women who did not succeed in getting pregnant with their first child revealed more anxiety and depression in childless women (F=4.58; p=.03 for anxiety and F=8.04; p<.01 for depression).

Discussion

This study followed up a cohort of women who underwent IVF treatment.

The most striking result was that anxiety and depression were found at follow-up to return to baseline levels after an initial increase during treatment in women who did not give birth after treatment. Treatment resulting in a live birth was found to result in a more positive long-term emotional status. New life goals and already having a child before treatment started were found to be associated with lower levels of anxiety and depression.

A limitation of the study is the high drop-out rate at various stages during the treatment, which resulted in a limited complete dataset. Furthermore, a drop-out analysis revealed higher levels of drop-out in women who did not give birth to a child. Despite these limitations, this was the first time a large cohort was studied before, during and after treatment. This enabled us not only to analyze the course of anxiety and depression, but also to investigate the women's attitude to childlessness and possible further treatment after abandoning IVF.

Longitudinal follow-up studies, as indicated, are scarce. Cross-sectional follow-up studies of the emotional status of involuntarily childless women and women with children indicate no important differences between these groups (Hammerberg et al. 2001, Leiblum et al. 1998, Weaver et al. 1997). This is in line with the present

longitudinal study, which shows no differences in the emotional status of the women before treatment started and several years after unsuccessful treatment. However, the women who gave birth to a child after treatment showed a more positive emotional status compared to the baseline. This indicates a positive effect of pregnancy and motherhood on emotional status for women with fertility problems. This is supported by studies in definitively childless women, who showed comparable emotional status but less life satisfaction than women with children (Leiblum et al. 1998; Singh & Williams 1981).

The availability of psychological counselling services was indicated as being vitally important at times of distress. It was indicated that ongoing counselling should be part of having IVF treatment and that the clinic should contact couples between treatments, since only a small proportion of the women availed themselves of the counselling services beyond the initial mandatory counselling session. On the other hand, it was already known that the most distressed patients fail to initiate contact with counsellors (Boivin et al. 1999). There should therefore be a reassessment of each couple's feelings and degree of psychological distress after each IVF cycle (Guerra et al. 1998). Couples should be made aware that unsuccessful IVF treatment is associated with increased levels of anxiety and depression after treatment (Verhaak et al. 2001; Baram et al. 1988), and that this is a normal response and the effect is still present six months after the last IVF cycle (Verhaak et al. 2005; Slade et al. 1997).

Furthermore, successful IVF was also found to be associated with increased levels of anxiety in comparison with women who had conceived naturally (Hjelmstedt et al. 2003). Levels of stress related to parenthood, on the other hand, were found to be equal whether women had conceived with or without IVF (Hjelmstedt et al. 2004). Although it was found that long-term emotional well-being was not affected by the fact of a live birth child, approximately 15% of the women whose treatment did not result in a live birth reported clinical levels of anxiety and/or depression. A strong relationship was found between emotional distress and mode of adaptation, since pursuing a desire for pregnancy was found to be associated with higher levels of anxiety and depression.

The clinical implication of the findings of this study points in the direction of additional support at the time people are abandoning treatment. Persisting with treatment options seems to negatively effect adaptation to childlessness because of an enduring uncertainty that results in a lack of control (Daniluk, 2001). Clinicians

could address the issue of abandoning treatment in their final consultations and inform patients about the emotional consequences of letting go their attempts to get pregnant. Indicating that grief is a natural response might help patients to understand their emotions. In addition, the prospect of most women adjusting well after several years might encourage women to give up treatment and focus on other life goals. However, psychosocial support during the decision process after IVF is still a relatively uncharted area. Further research is needed to shed more light on the process of leaving treatment and focusing on other life goals.

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10

Epilogue

Partly based on 'Psychological interference in in vitro fertilization treatment'

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Technical advances and economic prosperity have led to an optimistic society, where individual hopes, wishes and choices are more important than ever. In a health care setting we are generally being faced with an increasingly well-informed clientele, who expect to be successful. Failure is not an option, not in daily life, not in medicine. In general doctors go along with, or even stimulate this way of thinking. Prognostic models were launched that seem to enable individual counselling, for instance regarding their chances of success. Pre-treatment indicators of outcome and seemingly better treatment regimes are regularly introduced, stressing the feeling that the future can be predicted and shaped as pleased.

Postponement of having a first child has led to increased subfertility and a bigger demand for assisted reproductive techniques. Once IVF is the treatment of choice, couples tend to overestimate their individual chances of success prior to the start of treatment. This observation is probably due to a self protective mechanism, maybe due to lack of information, but surely as a reflection of optimism. After treatment has begun it is not only the physical hardships of treatment have to be dealt with, but an unsuccessful outcome is often not realistically anticipated. Consequently, the unsuccessful couples are left alone with nothing but shattered dreams which may continue into the long term. The present thesis is aimed at studying IVF by focussing on a stepwise integration of biomedical and psychological factors to describe the IVF treatment. In addition, the consequences and implications for daily practice are being discussed.

In the first part of this thesis existing and new prognostic biomedical factors in IVF were studied. Given the enormous amount of research being done in this particular field, this is a logical starting point to study IVF. First a landmark model was validated and it was shown that this model is not applicable nor usable in the daily clinical practice (of our hospital). The factors presented did not give additional information about the prognosis for the vast majority of the patients, suggesting that the model could not explain the variance of the outcome sufficiently. Models were once more found to be population specific and the application of a model to individuals of another population, remains, to say the least, unsatisfactory.
The next step was to study other pre treatment factors that were launched the last decade claiming additional prognostic capacity with respect to treatment outcome.

None of the biomedical, ultrasound and hormonal factors had predictive capacity (and consequently no explained variance) with respect to pregnancy after treatment. Finally, a new potential marker, FSH-isoforms, were explored with respect to their predictive capacity towards the outcome of IVF. Although very promising from a theoretical point of view, it was found that it is unlikely that this factor is predictive of the outcome.

In summary, we were not able to predict outcome in a relevant manner per individual. Therefore, we should consider ceasing to pretend we can, and therefore not exclude patients from treatment based merely on these tests. Ovarian reserve tests, if applied, should be reserved for a 'high risk' population, since they are not suitable to screen the general population. Criteria that could justify screening include; female age older than 35, unexplained infertility (regardless of age), family history of early menopause, previous ovarian surgery, chemotherapy, radiation, smoking and earlier poor response to exogenous gonadotropin stimulation (Speroff and Fritz eds).

Grossly abnormal test results could give more prognostic information and can help to guide the choice of treatment. Patient and doctor focus groups might be used to determine a clinical relevant cut off point by using a trade off scenario (more extreme cut-off values lead to better prognostication, but consequently to lower numbers of patients that can be prognosticated). But in the end, one cannot predict who will be among those few with abnormal test results that succeed, since a binominal prognostication (0 or 100%) is an utopia.

Exclusion from further treatment is therefore better based on clinical data, since a trial of treatment is the only way to identify the women that have a (small) chance of pregnancy. From this point of view, the first cycle might be considered a diagnostically one, as a part of the integral infertility evaluation (as proposed by the research group of te Velde et al. Utrecht, the Netherlands). However, the reimbursement system in the Netherlands was revised recently. This now in fact punishes couples that undergo only one cycle of IVF, since only the second and third cycle are reimbursed.

In the second part of the thesis psychological factors and biomedical factors were integrated in a holistic model to look for additional explained variance with respect to the outcome. Pre-existing psychological factors were found to be independently related to treatment outcome in IVF. This underlines the fact that psychological

factors could well be a co-factor in the chance of pregnancy after treatment. A significant effect was found, triggering to do further research regarding the mechanisms involved. However, the explained variance with respect to pregnancy chance was limited.

Not only pregnancy, but also dropout was being explored as outcome measure. Dropout rates were found to be related to psychological factors. But also voluntary withdrawal was found to be an important factor in dropout, indicating individual freedom of choice during fertility treatment. Avoiding treatment, or discontinuing treatment and maintaining the option of returning to treatment was hypothesized as a way of couples to protect their fragile dreams and avoid further painful failures (Penzias 2004).

Next, the relation between psychological factors and pregnancy after IVF was explored within a subgroup. In women with successful treatment lower concentrations of adrenaline were found at ovum pick-up, also lower concentrations of adrenaline and nor-adrenalin were found at embryo transfer, in comparison to unsuccessful women. The significant association of lower adrenaline concentration with pregnancy and with depression suggested that this adrenal hormone could be one of the links in the complex relationship between psychosocial stress and outcome after IVF. In line with the findings of the questionnaire-based study the clinical relevancy was less clear as a large overlap was found between successful and unsuccessful treatments. Consequently, it was not possible to define a specific cut off point.

In the third part of the thesis the consequences of IVF treatment on the psychological outcome were explored. In this part it was found that women showed an increase in both anxiety and depression after unsuccessful treatment. Since negative emotions seemed to disappear immediately after successful treatment, it was cautiously concluded that the stress of treatment is mainly determined by the threat of failure. Personality characteristics, preconceptions of the fertility problems and social support have been shown to determine the adjustment to unsuccessful IVF in women. This might allow early identification of women at risk for developing high levels of distress along with more tailored interventions.

Six months after unsuccessful treatment, no improvement in the levels of anxiety and depression were evident. Moreover, at follow-up more than 20% of the women showed sub-clinical forms of anxiety and/or depression. It was concluded that most

women adjust well to unsuccessful treatment, but six months after the last treatment cycle a considerable part still showed substantial emotional problems. As a result a long term follow-up study was conducted, where the majority of the unsuccessfully treated women were again found to adept well psychologically. Regarding the whole group, anxiety and depression were found to return to baseline levels following unsuccessful treatment at long term (at least three years) follow-up. Although the high dropout rates during the study prevent firm conclusions and taking into account that selective dropout can never be excluded, still the results were reassuring.

New life goals as a mode of adaptation were found to be related to lower levels of anxiety and depression in unsuccessful couples at follow-up. It is another contribution to the idea that long term psychological issues should be considered in becoming an integral part of general infertility care, as stated by Domar et al. (2004), but should also be considered in evaluating treatment outcome of IVF in particular. The findings may indeed lead to certain awareness in patients and colleagues, but also in health economists and policy makers, as this is vital for the funding of future care, interventions and additional research in this particular field.

Successful treatment was found to result in a more positive emotional status six months after the IVF-cycle and was also found to persist at least three years later. This implies that it is not only successful treatment, but also having a child that leads to less anxiety and less depression, compared with the situation prior to treatment. Remarkable findings since IVF children bring along the same worries and are generally raised and treated in the same manner as other (not IVF) children (Barnes et al. 2004). This suggests no need for concern, for example about the issue of disclosure to the child (Greenfeld et al. 1996) and might be attributed to more satisfaction within the partnership (Ulrich et al. 2004).

Future research

Although this project is the first prospective, longitudinal study that integrates biomedical, gynaecological and psychological issues in a large cohort of women undergoing IVF, more data would obviously have led to more robust conclusions and the large dropout rate over time is an inherent, but methodological problem. Obviously, since correct prediction of the outcome of IVF treatment is unlikely with the current perceivable factors, the search for other, more accurate predictors

deserves our attention. However, from a clinical point of view a sceptical approach towards new predictors seems justified, as a prediction model which will give more insight (with clinical relevancy) into the prognosis of an individual patient, is still non-existent.

The complex interplay between biomedical and psychological aspects of IVF treatment and the mechanisms, with particular respect to stresshormones, was a specific part of this thesis. Ideally, the combination of all known factors involved, i.e. hormonal, immunological, lifestyle and environmental in a prospective follow-up manner with more or less continuous measurements without dropout, would shed more light on these matters. Unfortunately this would imply that very large numbers of IVF patients would have to be studied in a 'test tube' setting, which is neither feasible nor desirable.

Most women were found to adapt well to (un)successful IVF. However, one subgroup was found that seemed to be at risk of developing severe emotional problems at least three years after the last treatment cycle. The adaptation process to the treatment as a whole should be focussed on. Notably the transitional process from trying to get pregnant into giving meaning to ones life without a genetically own child, needs further prospective evaluation. Predicting those who develop problems is obviously difficult, but taking the impact into account this group deserves our full attention. Whether again this group (about 15% show (sub)clinical forms of anxiety and/or depression) would benefit from psychological interventions needs to be explored. Interventions could not only enhance or shorten the natural recovery process, but also lower the number of patients with anxiety and/or depression. Currently an intervention study using internet tools is being launched in our clinic to look into these matters.

Clinical implications

The well-being of the couples needs to be constantly in our focus. Treatment success is obviously important and success rates need to be optimal within certain boundaries. One has to bear in mind however that couples willingly undergo the hardships of treatment to strive for pregnancy.

The boundaries need to be established together with the well-informed couple. The stimulation protocol, single embryo transfer and number of treatment cycles are mandatory items during the initial visit of the couple. These seemingly contradicting

aspects with respect to the outcome of treatment need special attention, as the reimbursement of up to three IVF treatment cycles were abolished in January 2004. Patients nowadays have to pay the first out of three IVF cycles themselves (unless otherwise insured) and as a result economical arguments seem to be more important than medical know-how. Whether this leads to a selection of better motivated couples or couples with a better prognosis is hypothetical.
The new market based health system that was introduced in January 2006 in the Netherlands could even induce further detrimental health consequences in IVF treatment, since a focus shift is stimulated from quality to quantity. Increased competition could undermine the solidarity of the system, letting the unsuccessful patient pay the price for lean health care in the end. Patients with a poor prognosis could even be faced with exclusion from treatment in the future. Maybe we should advocate more clearly that we are 'doctors with limits' (Braat 2002), also considering this aspect of patient care.

Participation of the couple in the decision taking process and more transparency of the treatment can enforce the feeling of self-control in couples, for instance by enabling internet access and as a result, low barriers to contact the treatment team (Haagen et al. 2003). Whether couples take on an active or a passive role in their own treatment for better coping is at their own choice, but their involvement needs to be triggered.
Should we interfere? Intervention of the mental health team could be been as a way to optimise treatment, but also as an interference in a possibly self-protective process (Smeenk et al. 2004). Whether interference leads to higher rates of treatment success, lower dropout rates, or prevention of long term depression needs further exploration.
Prior to treatment a 'pre-IVF-visit' to the doctor could be helpful to establish more clearly the boundaries of treatment and to present a clear and honest picture of the treatment, thereby avoiding misconceptions and pointing out alternative ways of adaptation. As a result of this thesis already a pre-IVF-visit has already been introduced as part of the standard IVF-protocol in our hospital.
Furthermore, during treatment doctors should be sensitive to patient`s perceptions regarding the treatment. This could be discussed during treatment, but should at least be addressed in a scheduled visit following each treatment cycle, succesfull or

not. If (sub) clinical forms of anxiety and/or depression are being suspected, referral to an IVF-team psychologist should be discussed and advised with the couple.
If a couple is on the waiting list and does not respond to the availability of starting treatment, a visit to a doctor might be offered to discuss the motives of postponement. In our clinic couples are contacted one year after unsuccessful treatment. We believe that this is not detrimental for their well-being or undermining their protective measures, but a reminder of the possibilities still available. Couples that want to maintain the option of returning to treatment can indicate that, without being forced to undergo treatment within a certain timeframe. After the last treatment cycle a concluding visit to the doctor should be an integral part of treatment and at that time it needs to be established whether couples might benefit from additional counselling following this visit. During this visit patients should also be informed that new life goals are associated with less distress in unsuccessful couples at long term follow-up.

Overall we believe that the patient's mental health should be considered an integral component of infertility care. A focus shift from the pure biomedical towards a broader approach could be strived for in order to improve the quality of care. In considering the whole treatment, as proposed by Heijnen et al. (2004) the 'term singleton birth rate per started IVF treatment in the overall context of patient discomfort, complications and costs' was introduced, which still seems limited to describe all aspects of treatment.

More attention to the psychological repercussions of infertility treatment could surely lead to a more personalised approach and to improvement in patient satisfaction. The availability of a multidisciplinary team that holistically integrates medical and mental health during the treatment period, which extends over the period of regular appearances in the clinic, would be the first step.

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Summary

Chapter 1

General introduction and outline of the thesis.

In the thesis three research goals are being dealt with:

1. Study existing and new prognostic biomedical factors in IVF
2. Study the integrated model of psychological and biomedical factors and the mechanisms involved on the course and outcome of IVF
3. Study the consequences of IVF on the psychological outcome and discuss recommendations for the future

Chapter 2

In this chapter a study is presented in which we externally validated the prognostic model presented by Templeton (1996) for a live birth resulting from IVF treatment. Data were used from the University Hospital, Nijmegen, the Netherlands, from March 1991 to January 1999. The predictive capacity of the model in our population discriminated between a group of women that had a low probability of success and that had a relatively high probability. Despite these encouraging findings, our data show that implementation of the model in clinical decision making remains difficult. The 'Templeton' model is not applicable nor usable in daily clinical practice, because the model did not give more information about the prognosis for the vast majority of the patients. The search for better prognostic factors resulting in better predictive models should therefore continue.

Chapter 3

In this chapter a relative new marker, Antimullerian hormone (AMH) was compared with other alleged predictors of treatment outcome. On day three of the cycle preceding the first IVF cycle several factors were assessed. In 112 consecutive IVF cycles, 40 viable pregnancies were achieved (36%). These 40 patients were compared with 40 randomly selected women out of the 72 remaining women without a pregnancy. None of the biomedical, echoscopic and hormonal factors showed predictive capacity with respect to pregnancy after treatment. AMH concentrations in serum proved to be the best predictor of ovarian responsiveness. However, a large variation was observed in AMH concentrations which limit the clinical applicability.

Chapter 4

In this chapter the predictive value of FSH-isoforms for the outcome of IVF treatment was analysed. We hypothesized that not the quantity, but the quality of basal FSH would be predictive. In order to test the hypothesis two 'extreme' groups were compared; a relatively young group with normal basal FSH levels and a good response to 150 IU of recombinant FSH and a relatively old group with normal basal FSH levels and a poor response to 300 IU of recombinant FSH. No statistical differences could be found in the isoform-composition between the two groups. Differences were found in the number of antral follicles and Inhibin B concentration in blood collected before the treatment. Although this pilot study comprises only ten patients, we conclude that it is not likely that FSH-isoforms predict treatment outcome after IVF

Chapter 5

In this chapter a study aimed to clarify the role of depression and anxiety on the outcome in assisted reproductive treatment is presented. Previous studies on this topic have shown contradicting results, which may have been caused by population characteristics, the design of the study, or small sample sizes. In a multicentre prospective study 281 out of 359 (81%) consecutively invited women were willing to take part. Before down-regulation by means of GnRH-analogues in a long IVF-protocol, patients were asked to fill out the Dutch version of the State and Trait Anxiety Inventory to measure anxiety and the Dutch version of the Beck Depression Inventory (BDI) to measure depression. Pre-existing psychological factors were found to be independently related to treatment outcome in IVF and should therefore be taken into account in patient counselling. Psychological factors may be improved by intervention, whereas demographic and gynaecological factors cannot.

Chapter 6

In this chapter a study was presented in order to gain more insight into psychological aspects of dropping out in IVF. In a prospective cohort study, 380 women entering their first treatment cycle of IVF or ICSI were enrolled. Standardized psychological questionnaires were administered before the start of the treatment and after treatment. Base-line psychological factors and the probability of dropout after IVF treatment were found to be associated in the group that stopped treatment for psychological reasons. Those who were denied further treatment by

the medical team, the 'actively censored' group, did not show pretreatment differences regarding psychological measures in comparison with those who continued treatment. After treatment, the group that was denied further treatment showed higher levels of anxiety and depression compared to those that continued. Dropout, being a well-known phenomenon in IVF, was found to be related to pre-existing psychological factors in IVF.

Chapter 7

In this chapter a study was presented that examined the associations between the stress hormones adrenaline, noradrenaline and cortisol in urine during treatment with the self reported stress, in order to investigate the mechanism for the previously observed negative association of anxiety and depression with the outcome of IVF. In a multicentre prospective cohort study, 168 women entering their first cycle of IVF treatment were enrolled. From each participant three nocturnal urine samples were collected; pre-treatment, before ovum-pickup (OPU) and before embryo-transfer (ET). Additionally, two questionnaires were administered before the start of the treatment to measure anxiety and depression. A significant positive correlation between urinary adrenaline concentrations at baseline and ET and the scores on depression at baseline were found. In women with successful treatment lower concentrations of adrenaline at OPU and lower concentrations of adrenaline and noradrenaline at ET, compared with unsuccessful women, were found. The significant association of adrenaline concentration with pregnancy and with depression suggested that this adrenal hormone could be one of the links in the complex relationship between psychosocial stress and outcome after IVF.

Chapter 8

In this chapter study into the course of the emotional response to IVF from pre-treatment to six months post-treatment and factors that contributed to that course was presented. In a longitudinal prospective study 148 IVF patients and 71 partners completed self-report questionnaires. Assessments of anxiety and depression were repeated immediately following the final treatment cycle and again six months later. Women showed an increase of both anxiety and depression after unsuccessful treatment and a decrease after successful treatment. Men showed no change in anxiety and depression neither after successful nor after successful

treatment. In the six months after unsuccessful treatment, women showed no recovery. At follow-up, more than 20% of the women showed sub-clinical forms of anxiety and/or depression. Personality characteristics, meaning of the fertility problems, and social support determined the course of the emotional response, which allows early identification of women at risk as well as tailored interventions.

Chapter 9

In this chapter a prospective cohort study was presented aiming at of the gain of more insight into long term psychological adjustment to unsuccessful treatment in IVF. Two-hundred-ninety-eight women (78% of the participants) completed the last set of questionnaires 3 to 5 years after treatment. 193 women were successful in achieving a pregnancy, 105 women were unsuccessful. Anxiety and depression were found to return to baseline levels following unsuccessful treatment at follow-up after an initial increase during treatment. On the other hand successful treatment was found to result in a more positive long term emotional status. New life goals as mode of adaptation 3 to 5 years after IVF were found to be related to lower levels of anxiety and depression at that time. The majority of the unsuccessfully treated women were found to psychologically adept well. Positive adjustment was related to developing new life goals in contrast to persisting in attempts to get pregnant.

Chapter 10

In this chapter an epilogue is presented with some concluding remarks regarding the studies presented. Clinical applicability of the findings and recommendations for future research are being discussed. It was concluded that more attention to the psychological repercussions of infertility treatment could lead to a more personalised approach and to improvement of patient's satisfaction. The availability of a multidisciplinary team that holistically integrates medical and mental health during the treatment period, which extends the period of regular appearances in the clinic, would be the first step.

Hoofdstuk 1

Algemene inleiding en indeling van het proefschrift. In het proefschrift worden drie onderzoeksdoelen behandeld;

1. Bestaande en nieuwe prognostische biomedische factoren in IVF onderzoek
2. Een geïntegreerd model bestuderen van psychologische factoren en biomedische factoren op het beloop en de uitkomst van IVF
3. De gevolgen van IVF behandeling op de psychologische uitkomst onderzoeken en aanbevelingen voor de toekomst bespreken

Hoofdstuk 2

In dit hoofdstuk wordt er een studie gepresenteerd waarin het prognostische model voor een levendgeborene na IVF, zoals dat door Templeton is gepubliceerd (1996), extern wordt gevalideerd. Data werden gebruikt van de Radboud Universiteit, Nijmegen, Nederland, van maart 1991 tot januari 1999. De voorspellende capaciteit van het model in onze populatie maakte onderscheid tussen een groep vrouwen me een lage succeskans en een relatief hoge succeskans. Ondanks deze bemoedigende bevindingen, tonen onze data aan dat implementatie van het model bij het maken van klinische beslissingen moeilijk blijft. Het 'Templeton' model is derhalve niet toepasbaar of bruikbaar in de dagelijkse praktijk, omdat het model niet meer informatie gaf omtrent de prognose voor veruit het grootste deel van de patiënten. De zoektocht naar betere prognostische factoren wat zouden kunnen resulteren in betere voorspellende modellen dient daarom door te gaan.

Hoofdstuk 3

In dit hoofdstuk wordt een relatief nieuwe marker, het Anti-Mullerian hormoon (AMH) vergeleken met andere vooronderstelde voorspellers van de behandelingsuitkomst. Op dag drie van de cyclus voorafgaande aan de eerste IVF cyclus werden verscheidene factoren bepaald. In 112 IVF cycli kwam het tot 40 doorgaande zwangerschappen (36%). Deze 40 patiënten werden vergeleken met 40 patiënten welke random werden geselecteerd uit de 72 overige vrouwen zonder een zwangerschap. Van geen van de biomedische, echoscopische and hormonale factoren werd voorspellende waarde aangaande zwangerschap na behandeling aangetoond. Van AMH concentraties in serum werd gevonden dat deze de ovariële respons konden voorspellen, als enige van de onderzochte factoren. Een grote

variatie werd gevonden voor AMH concentraties, wat de klinische toepasbaarheid beperkt.

Hoofdstuk 4

In dit hoofdstuk is de voorspellende waarde van Follikel stimulerend hormoon (FSH)-isovormen m.b.t. de uitkomst van de IVF behandeling onderzocht. Onze hypothese luidde dat FSH niet zozeer kwantitatief alsmede kwalitatief voorspellend zou kunnen zijn m.b.t. de uitkomst van de behandeling. Om de hypothese te testen werden twee 'extreme' groepen vergeleken; een relatief jonge groep met normale basale FSH waarden met een goede respons op 150 eenheden recombinant FSH tijdens behandeling en een relatief oude groep met normale basale FSH waarden en een slechte respons op 300 eenheden recombinant FSH. Statistisch konden geen verschillen in de isovorm samenstelling tussen beide groepen worden gevonden. Verschillen werden gevonden in het aantal antrale follkels en Inhibine B concentraties in bloed dat werd verzameld voorafgaande aan de behandeling. Hoewel deze pilot studie slechts uit tien patienten bestaat, concluderen wij dat het niet waarschijnlijk is dat FSH-isovormen de uitkomst van IVF kunnen voorspellen.

Hoofdstuk 5

In dit hoofdstuk wordt een studie gepresenteerd welke is uitgevoerd om de rol van angst en depressie op de uitkomst van geassisteerde voortplanting te verduidelijken. Voorafgaande studies die zich met deze materie hebben beziggehouden hebben tegenstrijdige resultaten laten zien, welke kunnen zijn veroorzaakt door populatie kenmerken, studie opzet of kleine groepen. In een multicentre prospectieve studie waren 281 van de 359 benaderde patiënten (81%) bereid om deel te nemen aan het onderzoek. Voorafgaande aan de down-regulatie met behulp van GnRH analogen in een lang IVF-protocol, werden patiënten gevraagd om de State en Trait Anxiety Inventory en de Beck Depression Inventory (BDI) vragenlijsten in vullen om respectievelijk angst en depressie te meten. Vooraf aanwezige psychologische factoren bleken onafhankelijk gerelateerd aan de uitkomst van de IVF behandeling en zouden daarom betrokken moeten worden in de counselling van patiënten. Psychologische factoren kunnen wellicht beïnvloed worden door interventies, demografische en gynaecologische factoren echter niet.

Hoofdstuk 6

In dit hoofdstuk staat een studie beschreven die meer inzicht tracht te verschaffen over de psychologische aspecten van uitval tijdens IVF. In een prospectieve cohort studie werden 380 patiënten die voor de eerste behandelingscyclus van IVF kwamen geïncludeerd. Gestandaardiseerde psychologische vragenlijsten werden afgenomen voorafgaande aan de behandeling en na afloop van de behandeling. Baseline psychologische factoren en de uitvalskans na IVF bleken geassocieerd in de groep die aangaf met de behandeling te zijn gestopt om psychologische redenen.
De patiënten die verdere behandeling werd ontzegd liet voorafgaand geen verschillen op psychologisch gebied zien vergeleken met hen die de behandeling voorzetten. Volgend op de behandeling gaf de groep die verdere behandeling was ontzegd wel meer angst en depressie aan vergeleken met hen die doorgingen. Uitval, een bekend fenomeen tijdens de IVF behandeling, bleek gerelateerd aan voorafgaande psychologische factoren.

Hoofdstuk 7

In dit hoofdstuk wordt een studie behandeld die de relatie tussen de stress hormonen adrenaline, noradrenaline en cortisol in urine met de zelf aangegeven stress tijdens een behandeling onderzoekt om het mechanisme te onderzoeken voor de eerder beschreven negatieve associatie tussen angst en depressie en de uitkomst van IVF. In een multicentre prospectieve cohort studie werden 168 vrouwen die voor hun eerste IVF behandelingscyclus kwamen geïncludeerd. Van elke deelneemster werden drie nachtelijke urinemonsters verzameld; voorafgaande aan de behandeling, voorafgaande aan de punctie en voorafgaande aan de embryotransfer. Tevens werden twee vragenlijsten afgenomen voorafgaande aan de behandeling om angst en depressie te meten. Een significante positieve correlatie tussen de urinaire adrenaline concentraties voorafgaand aan de behandeling en embryotransfer en de depressie scores voorafgaande aan de behandeling werd gevonden. Bij vrouwen bij wie de behandeling succesvol was werden in vergelijking met de vrouwen waarbij de behandeling niet tot zwangerschap leidde lagere adrenaline concentraties ten tijde van de punctie en lagere concentraties adrenaline en noradrenaline ten tijde van de embryotransfer. De significante associatie tussen adrenaline concentraties met zwangerschap enerzijds en met depressie anderzijds geeft aan dat dit hormoon een van de schakels zou kunnen zijn in de complexe relatie tussen psychosociale stress en de uitkomst na IVF.

Hoofdstuk 8

Dit hoofdstuk beschrijft een longitudinale studie waarin de emotionele respons wordt beschreven op de IVF behandeling van voorafgaand aan de behandeling tot zes maanden na de behandeling waarbij de factoren die bijdragen aan dat beloop worden gepresenteerd. 148 IVF patiënten en 71 van hun partners vulden de vragenlijsten in. Angst en depressie werden direct volgend op de laatste behandelingscyclus gemeten en vervolgens zes maanden hierna. Bij vrouwen werden een toename van zowel angst als depressie gevonden volgend op niet succesvolle behandeling en een afname na succesvolle behandeling. Mannen toonden geen verandering in zowel angst als depressie of het nu wel of niet een succesvolle behandeling betrof. In de zes maanden volgend op de niet succesvolle behandeling werd er bij de vrouwen geen verbetering gevonden.

Ten tijde hiervan werd bij 20% van de vrouwen subklinische vormen van angst en/of depressie gevonden. Persoonlijkheidskenmerken, de betekenis welke gegeven wordt aan fertiliteitproblemen en sociale ondersteuning bepaalden het beloop van de emotionele respons. Dit stelt ons wellicht in staat om de vrouwen die at risk zijn vroeg te identificeren en passend te interveniëren.

Hoofdstuk 9

Een prospectieve cohort studie wordt in dit hoofdstuk gepresenteerd waarin getracht wordt meer inzicht te verkrijgen in lange termijn psychologische aanpassing aan onsuccesvolle IVF behandeling. De laatste set vragenlijsten werd 3 tot 5 jaar na de laatste behandeling door 298 deelneemsters ingevuld (78%). 193 vrouwen kregen een kind, 105 vrouwen niet. Angst en depressie bleken naar uitgangsniveau terug te keren volgend op onsuccesvolle behandeling na een in hoofdstuk 8 beschreven initiële stijging. Aan de andere kant bleek succesvolle behandeling te resulteren in een positievere emotionele status. Nieuwe levensdoelen zoals de aanpassingsmanier 3 tot 5 jaar na IVF bleken gerelateerd aan minder angst en depressie op dat moment. De meerderheid van onsuccesvol behandelde vrouwen bleek zich psychologisch goed aan te passen. Positieve aanpassing bleek gerelateerd aan het ontwikkelen van nieuwe levensdoelen, het persisteren in het proberen om zwanger te raken bleek hier haaks op te staan.

Hoofdstuk 10

In dit hoofdstuk wordt een epiloog beschreven met enkele concluderende opmerkingen betreffende de gepresenteerde studies. Klinische toepasbaarheid van de bevindingen en aanbevelingen voor toekomstig onderzoek worden besproken. Meer aandacht voor de psychologische repercussies zouden tot een meer persoonlijke benadering en tot toename van de tevredenheid van patiënten aanleiding kunnen geven. De beschikbaarheid van een multidisciplinair team dat zowel aandacht heeft voor medische en geestelijke aspecten van de behandeling, zowel tijdens maar ook na de periode waarin de kliniek regelmatig wordt bezocht, zou de eerste stap zijn.

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Curriculum Vitae

Jesper Smeenk werd op 24 februari 1973 geboren te Didam.
In 1991 behaalde hij zijn VWO diploma aan het Rhedens Lyceum te Rozendaal.

Vervolgens startte hij met de studie Geneeskunde aan de Katholieke Universiteit Nijmegen (1991-1998). Tijdens deze studie werden er enkele stages gevolgd; 1995 Coïmbra Portugal, 1996 München Duitsland, 1998 Sengerema Tanzania.
Interesse voor onderzoek werd gevoed door een wetenschappelijke stage op de afdeling Obstetrie/Gynaecologie in het UMCN in 1997.

Na het behalen van het arts examen werd er in 1998 gestart met het project 'Stress en IVF', hetgeen resulteerde in dit proefschrift. Daarnaast participeerde hij als arts-onderzoeker in enkele 'hormone replacement therapy' trials.

Vervolgens begon hij in 2002 als assistent geneeskunde niet in opleiding (AGNIO) in het Canisius Wilhelmina Ziekenhuis, om in datzelfde jaar te starten met de opleiding Gynaecologie.

In oktober 2005 trouwde hij met Petra Beulen, op 2 augustus 2006 kregen zij een zoon Jorn.