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# **Emotional impact of unsuccessful fertility treatment in women**

Christianne Verhaak 2003



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# **Emotional impact of unsuccessful fertility treatment in women**

Een wetenschappelijke proeve op het gebied  
van de Medische Wetenschappen

## **Proefschrift**

ter verkrijging van de graad van doctor aan de  
Katholieke Universiteit Nijmegen  
op gezag van de Rector Magnificus Prof.Dr. C.W.P.M. Blom,  
volgens besluit van het College van Decanen  
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door

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# Chapter 1

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General Introduction



## GENERAL INTRODUCTION

One out of every 55 children born in the Netherlands is conceived through in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) (Kremer et al., 2002). These artificial reproduction treatments comprise in vitro fertilization of the oocyte, i.e. outside the body. In IVF, oocytes are retrieved from the ovary and brought into a petri dish, where sperm is added. Accordingly, the actual fertilization takes place more or less spontaneously. ICSI treatment consists of the same egg-collection procedure, but in the laboratory per oocyte, one sperm is selected and injected into the oocyte and the actual fertilization occurs more artificially.

The percentage of couples with fertility problems has remained stable for several years at about 13% (Henning & Strauss, 2002; Van Balen et al., 1997; Litt et al., 1992; Stanton & Dunkel-Schetter, 1991), whereas the percentage of couples taking advantage of IVF or ICSI treatment has increased considerably in the last decade (Kremer et al., 2002). At the University Medical Centre St Radboud, approximately fifty percent of the women who have started IVF or ICSI treatment have conceived within one year. This means that for a considerable number of couples treatment will be unsuccessful. For them, there are very few possibilities for further treatment. Nearly all of them will have to adjust to life without children of their own. It is precisely this notion of a 'last chance' that magnifies the emotional stress of IVF and ICSI treatment in comparison to other fertility treatments (Litt et al., 1992; Dennerstein & Morse, 1988). The stress of infertility is also reflected by the fact that half of the women experience fertility problems as the worst event that has ever happened to them (Mahlstedt, 1985).

IVF and ICSI treatment may consist of several cycles. In the Netherlands, health insurance companies cover a maximum of three treatment cycles per ongoing pregnancy. For any additional treatment cycle, the couples themselves will have to meet their own expenses. One cycle takes about eight weeks. It starts with a period of hormonal suppression and stimulation brought about by self injections, which is followed by a period of follicle growth monitoring. When enough follicles are matured, oocyte retrieval takes place, which may be followed by the actual in vitro fertilization. In the event of fertilization, a maximum of two embryos is transferred into the womb three days after retrieval. Three weeks later, a pregnancy test can be performed. If the treatment cycle is unsuccessful, a new treatment cycle

can be started after one natural cycle. The mean number of treatment cycles is nearly two treatment cycles (range 1 to 6).

The emotional aspects of fertility problems in general and, more specifically, of unsuccessful IVF or ICSI treatment have received a great deal of attention. Studies generally support the considerable emotional stress as a response to unsuccessful treatment (for reviews see: Eugster & Vingerhoets, 1999; Edelmann, 1990; Wright et al., 1989). However, most of these studies have been cross-sectional. The few longitudinal studies that were performed had only two assessment points, before and after one IVF or ICSI treatment cycle (Visser et al., 1994; Connolly et al., 1992; Hynes et al., 1992; Newton et al., 1990), suggesting an increase in distress after an unsuccessful treatment cycle. When different indicators of distress such as anxiety and depression have been assessed, studies have particularly revealed increased levels of depression after one unsuccessful treatment cycle (Beaurepaire et al., 1994; Berg & Wilson, 1991). However, since most women undergo more than one treatment cycle (Emery et al., 1997), only long term longitudinal studies with several assessment points and various distress indicators can provide comprehensive information about the course and intensity of the emotional response during the entire course of treatment. In addition, this type of design will provide an answer to the clinically relevant issue regarding the number of women developing serious emotional problems as a consequence of IVF or ICSI treatment. It is important to gain insight into factors contributing to the course of the emotional response, particularly for this potential group of distressed women. The few studies that have focussed on this issue (Terry & Hynes, 1998; Litt et al., 1992) were limited to the emotional response to one treatment cycle. Factors that contribute to the long term emotional response have not yet been investigated.

The aim of this thesis is to fill in the gap in knowledge on the emotional response to both short term (after one treatment cycle) and long term (after consecutive treatment cycles) unsuccessful IVF and ICSI treatments and provide insight into the factors that contribute to its course.

Accordingly, the main research questions in this thesis are:

- a. What is women's short and long term emotional response to unsuccessful IVF or ICSI treatment?
- b. What factors contribute to women's short and long term emotional response to unsuccessful IVF or ICSI treatment?

To gain insight into the answers to these research questions, we used a longitudinal study design with three assessment points between the time before starting the first treatment cycle to six months after ceasing treatment. A comprehensive set of variables was taken into account to assess factors contributing to women's emotional response after unsuccessful treatment. In addition to these main questions, we also examined the course of both women and men's satisfaction with their marital and sexual relationship, men's emotional response to unsuccessful treatment, and women and men's emotional response after successful treatment.

The following section describes the hypothesized course of women's emotional response to unsuccessful treatment, factors expected to contribute to the course, the study design and the different parts of the thesis.

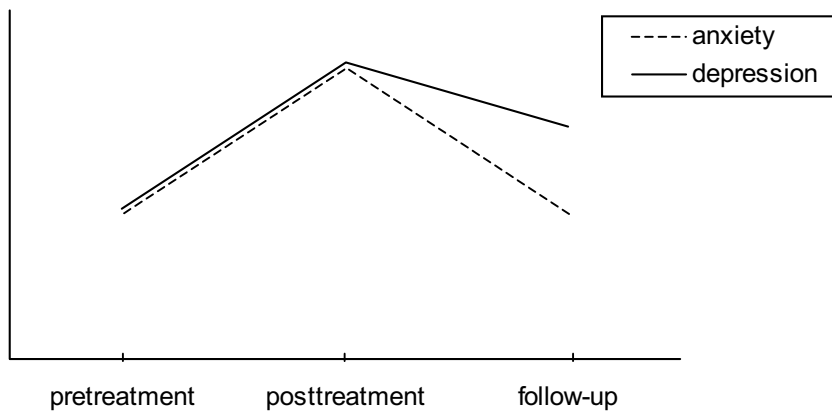
### **Course of the emotional response**

Infertility is a chronic stressor, consisting of a chain of events that frequently endures for several years (Domar et al., 1993) and can be characterized as threat, uncertainty, uncontrollability and loss (Dunkel-Schetter & Lobel, 1991). The threat may be the result of the treatment itself, which includes several physically and emotionally strenuous aspects, but it may also result from an inability to fulfil an important life goal. In addition, there is the uncertainty and uncontrollability of the outcome of fertility treatment. The main stressor is the possibility rather than the reality of infertility: 'There is nearly always a degree of ambiguity about the outcome' (Dunkel-Schetter & Lobel, 1991). These aspects of threat, uncertainty and uncontrollability may easily evoke anxiety (Stanton & Dunkel-Schetter, 1991). Uncontrollability may also result in depressive feelings (Seligman, 1975). When the treatment does not finally result in pregnancy, loss will become apparent and may also lead to depressive feelings.

Longitudinal studies make it possible to investigate the course of anxiety and depression during consecutive phases of treatment. Information about possible differences in the course of anxiety and depression is important for understanding the process of the emotional response to IVF and ICSI treatment. In the end, this will provide an opportunity to tailor any

psychological interventions to negative emotions that are evident in different phases of the treatment.

In line with previous studies and corresponding to our description of the stressor of fertility problems in terms of threat, uncertainty, uncontrollability and loss, hypotheses were formulated for the courses of anxiety and depression during consecutive phases of treatment. Figure 1 presents the hypothetical courses of women's anxiety and depression in the event of unsuccessful treatment.



**Figure 1.** Hypothetical courses of anxiety and depression after unsuccessful IVF or ICSI treatment

A continuous increase is expected in both anxiety (because of the continuing threat of possible consecutive cycles) and depression (because of the enduring uncontrollability of the treatment outcome and the negative outcome in the first cycle) from pretreatment to posttreatment after consecutive unsuccessful cycles. After the last cycle, anxiety is expected to decrease to pretreatment levels due to the end of both the threat of treatment and the uncertainty of the outcome of treatment. In contrast, because women have to adjust to losing the possibility of pregnancy, depression six months after the final cycle is expected to be even higher than pretreatment levels.

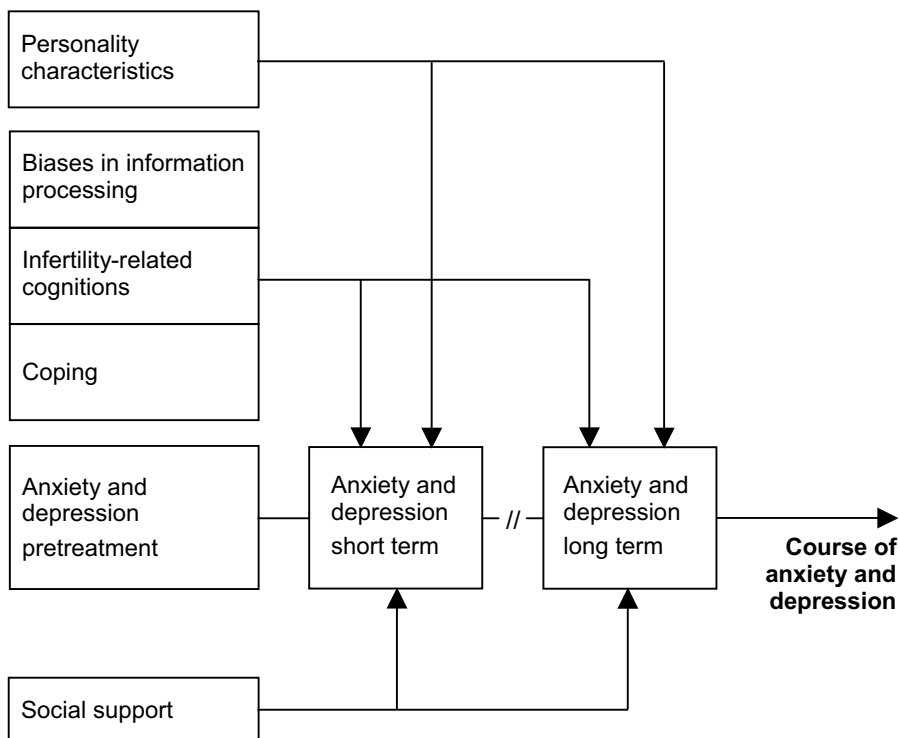
Another important aspect of the treatment is its impact on the marital and sexual relationship. Couples indicated that their relationship with their partner is the most important source of social support when dealing with their fertility problems (Laffont & Edelmann, 1994<sup>a</sup>). Social support is a significant protective factor in relationship to the development of anxiety and depression following a stressful experience (Holahan et al., 1996). Accordingly, a relatively high level of dissatisfaction with the relationship would make couples more vulnerable to developing emotional problems in the event of unsuccessful treatment. Previous studies on the marital relationship in couples facing fertility problems have been cross-sectional or focussed on only one treatment cycle (Visser et al., 1994; Berg & Wilson, 1991). That is why in the present thesis we also explored the course of satisfaction with marital and sexual relationships in couples during the treatment.

### **Factors that contribute to the course of the emotional response to unsuccessful treatment**

The investigation of factors that contribute to the course of women's emotional response to unsuccessful IVF and ICSI treatment is based on stress vulnerability models, which were originally developed to predict anxiety and depression in the general population and applied in a wide range of clinical and medical populations. These models consider personality characteristics (Clark et al., 1994), biases in information processing (Mogg & Bradley, 1998; Williams et al., 1996), general or stressor-related cognitions (Alloy et al., 1999; Beck & Clark, 1997), coping (Holahan et al., 1996; Lazarus & Folkman, 1984) and social support (Cohen & Wills, 1985) as important factors contributing to the emotional response to a severe stressor such as a fertility treatment. The few prospective studies on the emotional impact of IVF and ICSI treatment have found support for the importance of some of these factors, in so far as they were taken into account: for example, personality characteristics such as optimism as well as acceptance of the fertility problems were found positively related to a more favourable emotional adjustment to an unsuccessful treatment cycle (Terry & Hynes, 1998; Litt et al., 1992).

In the present thesis, we investigated the validity of a comprehensive stress vulnerability model in a fertility treatment setting, as presented in Figure 2.





**Figure 2.** Factors of the stress vulnerability model that are assumed to contribute to the course of anxiety and depression

Based on stress vulnerability models and previous studies on IVF and ICSI treatment, it was hypothesized that the personality characteristic of neuroticism, biases in information processing, cognitions of helplessness regarding the fertility problems, passive stress coping, a relatively low level of social support and dissatisfaction with the marital and sexual relationship contributed to a more negative emotional response to an unsuccessful treatment cycle. In addition, we expected the personality characteristics of optimism and extraversion, cognitions of acceptance of the fertility problems and active stress coping to abate the negative emotional response to unsuccessful treatment.

So far, differentiations have not been made in the hypotheses with respect to anxiety and depression. Although anxiety and depression are supposed

to be emotional responses to different aspects of the stressor of IVF or ICSI treatment, they are highly related and share common characteristics. There are several models that explain the common and distinct aspects of anxiety and depression. We mention three of these models.

- Firstly, there is the tripartite model (Clark et al., 1994), proposing that the corresponding part of anxiety and depression consists of negative affectivity; depression is also characterized by low positive affectivity.
- Secondly, there are information processing models, which propose that the aetiology of anxiety - but not of depression - is specifically based on attentional biases in information processing (Pury, 2002; Mogg & Bradley, 1998; LeDoux, 1996; Williams et al., 1996; MacLeod & Hagan, 1992; Foa & Kozak, 1986).
- Thirdly, there is the cognitive content model (Beck et al., 2001; Beck & Scott Perkins, 2001), which assumes that beliefs characterized by hopelessness and helplessness are important determinants of the establishment of depression).

When relating these three models to the previously described stress vulnerability models, negative affectivity in terms of neuroticism might be expected to be a risk factor for the development of both anxiety and depression, and optimism, extraversion and acceptance, as indications of positive affect, as protective factors in the development of depression. In addition, one might expect attentional biases to be risk factors for anxiety and cognitions of helplessness with respect to the fertility problems as risk factors for depression.

## **Design of the study**

### *Subjects*

The study sample consisted of women entering the fertility department at University Hospital St Radboud in Nijmegen, the Netherlands, in 1999 and 2000. All couples were going to start their first cycle of an IVF or ICSI treatment and with sufficient fluency in the Dutch language were eligible to participate (N=443). Three hundred and eighty women agreed to participate. Different selections of patients were used in different chapters. The analyses in *Chapter 2* were based on a preliminary sample<sup>1</sup> of 207

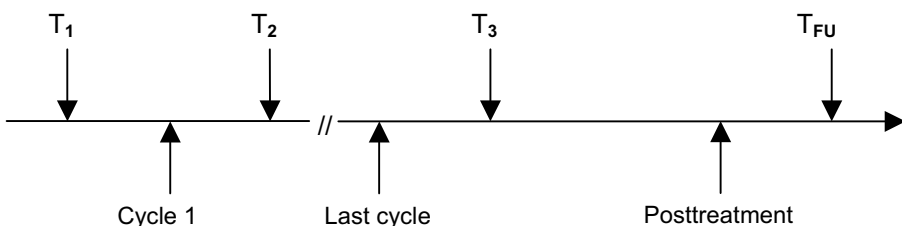
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<sup>1</sup> In the study in Chapter 2 patients of two hospitals participated (St. Radboud, Nijmegen: N=174, Baronie, Breda: N=33)

women who completed one assessment (127 of these women completed two assessments). *Chapter 3* is based on the final sample of 259 women (irrespective of treatment outcome) who completed the first two assessments. *Chapter 4* is based on a subsample of 49 women who participated in a Stroop experiment and completed the first and second assessments. In *Chapter 5*, only women with an unsuccessful first treatment cycle and two completed assessments were taken into account (N=187). Finally, complete datasets for three assessment points for anxiety and depression (pretreatment, after the last treatment cycle and six months after the last cycle), as presented in *Chapter 6*, were available for 148 women. Complete datasets were available for 86 women for satisfaction with the marital and sexual relationship (as presented in *Chapter 7*). These differences in the size of the datasets in Chapters 6 and 7 were due to a special recall procedure after the follow-up assessments, assessing solely treatment outcome, anxiety and depression for women six months after the last treatment cycle.

#### *Assessment points*

To investigate the course of the emotional response to IVF and ICSI treatment, the short and long term emotional response was taken into account. The short term emotional response was defined as the response to the first treatment cycle ( $T_2$ ). The long term emotional response was the response to the last treatment cycle ( $T_3$ ) and a follow-up six months later ( $T_{FU}$ ). The moments of measurement are indicated in Figure 3.



**Figure 3.** Assessment points and treatment phases

They took place before the start of the first treatment cycle, after the first cycle, after consecutive cycles, and six months after the last cycle. The first assessment point ( $T_1$ ) was prior to the start of the first treatment cycle, about one to two weeks before the start of medication. The second assessment point ( $T_2$ ) was four to six weeks after the first cycle pregnancy test. The third assessment point ( $T_3$ ) was four to six weeks after the last cycle pregnancy test. The follow-up assessment was six months after the last treatment cycle ( $T_{FU}$ ). A treatment cycle was retrospectively operationalised as the last cycle when a new cycle had not been started for the following 12 months. Accordingly, assessments took place after each consecutive cycle, but only assessments before the first, after the first, after the last, and six months after the last cycle were taken into account.

### **Part 1. Short term course of anxiety, depression and satisfaction with the marital and sexual relationship**

In the first part of the thesis, we investigated women's pretreatment emotional status and satisfaction with marital and sexual relationship upon entering IVF or ICSI treatment. Pretreatment anxiety, depression, and satisfaction with the marital and sexual relationship were compared to norm scores for same gender and age groups in *Chapter 2*. In addition, the course of emotional response to the first treatment cycle and the course of the marital and sexual satisfaction after one cycle were explored, just as differences between pregnant and non-pregnant women and between women entering IVF treatment and ICSI treatment.

In *Chapter 3*, the course of women's emotional response to the first treatment cycle and of marital and sexual satisfaction upon starting the first IVF or ICSI treatment was investigated. Men's emotional response and marital and sexual satisfaction were also taken into account. In addition, the relationship between the pretreatment intention for further treatment and the actual practice after one unsuccessful treatment cycle was explored.

### **Part 2. Factors that contribute to the short term course of the emotional response**

The second part of the thesis addressed the question of which set of factors contribute to the course of women's emotional response to the first

unsuccessful treatment cycle, the short term emotional response. In *Chapter 4*, we investigated the predictive value of biases in automatic information processing as contributors to the course of the emotional response to the first unsuccessful treatment cycle after controlling for neuroticism. We focussed on preattentive biases towards threatening information, which are assumed to be important factors in the development of anxiety.

In the *Chapter 5*, we investigated the strategic level of information processing. We tested a comprehensive model of factors that were assumed to contribute to the emotional response to an unsuccessful treatment cycle, including personality characteristics, cognitions of the fertility problems, coping and social support. In addition, demographic and clinical characteristics were incorporated into the model to control for the possible confounding effects of prognostic factors for the success of the treatment.

### **Part 3. The long term course of anxiety and depression, satisfaction with the marital and sexual relationship, and factors contributing to that course.**

In the third part, emphasis was put on the long term course of the emotional response and the long term course of satisfaction with the marital and sexual relationship. In *Chapter 6*, we studied the course of the emotional response between pretreatment assessment, posttreatment assessment and follow-up assessment six months after the last treatment cycle. Again we investigated possible differences in treatment outcome (pregnant or non-pregnant) and gender. In addition, the question of which factors contributed to the long term course of women's emotional response to unsuccessful treatment was addressed in chapter 6.

Finally, we studied the course of dissatisfaction with the marital and sexual relationship from the start of the first treatment cycle to six months after the last treatment cycle in *Chapter 7*. In addition, differences in treatment outcome (pregnant or non-pregnant) and gender were investigated.

The results were summarised in the last part of this thesis. The theoretical and clinical implications of the results were discussed and recommendations for further research were put forward.

# Part 1

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Short term course of anxiety,  
depression, and satisfaction with the  
marital and sexual relationship



## Chapter 2

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### Stress and marital satisfaction in women before and after their first cycle of in vitro fertilization and intra cytoplasmic sperm injection

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*Fertility and Sterility, 2001, 76, 525-531*





## **STRESS AND MARITAL SATISFACTION IN WOMEN BEFORE AND AFTER THEIR FIRST CYCLE OF IN VITRO FERTILIZATION AND INTRA CYTOPLASMIC SPERM INJECTION**

### **Abstract**

The objective of the study was to determine differences in emotional status (anxiety and depression) and marital satisfaction in women before and after their first cycle of IVF or ICSI, as well as differences in emotional status and marital satisfaction between the women who became pregnant and those who did not. A design with repeated measurement was used. Women completed the first questionnaire three to twelve days before the start of their first treatment cycle (N=207) and three weeks after their pregnancy test and (in the event of pregnancy) their first transvaginal ultrasound (N=127). The study took place in the fertility department at a university and a regional hospital. The main outcome measures were: state anxiety (STAI), depression (BDI), mood (POMS) and marital satisfaction (MMQ). The independent variables were: treatment outcome and type of treatment. The results indicated that at pretreatment, the women who became pregnant showed lower levels of depression than those who did not. Higher levels of depression in the pregnant women after the first cycle were due to higher scores on vital aspects of depression, related to signs of early pregnancy. Higher levels of depression in the non-pregnant women were due to a higher score on cognitive aspects of depression. Differences in emotional status between pregnant and non-pregnant women were present before treatment and became more apparent after the first IVF/ICSI cycle. There were no differences in emotional status between the women who underwent IVF and those who underwent ICSI.

### **Introduction**

Recent studies have shown a negative relationship between stress and fertility rates in general (Csemiczky et al., 2000) and between stress and the success rate of in vitro fertilization (IVF) (Thiering et al., 1993). Higher levels of depression (Thiering et al., 1993) or anxiety (Stoleru et al., 1999) seem to be related to lower pregnancy rates. The clinical relevance of these findings makes it necessary to consider ways of managing this stress and in doing so perhaps improve IVF or intracytoplasmic sperm injection (ICSI) pregnancy rates. Domar et al. (2000) showed a positive relationship between psychological interventions and pregnancy rates in women with a

short history of infertility (one to two years). The study did not provide any insight into the mechanisms that underlie the relationship between stress and fertility, and it did not focus on women treated by IVF or ICSI. From a psychological point of view, it would be worthwhile to gather detailed information about the characteristics of stress before and after an IVF/ICSI cycle, and about differences in stress levels and responses between women who become pregnant and those who do not.

Women who enter IVF/ICSI treatment have to deal with two types of stressors - the chronic stressor resulting from the threat of definitive infertility and the loss of future plans for having children (Boivin et al. 1995; Berg & Wilson, 1991) and the acute stressor resulting from the treatment itself. Each type of stressor may lead to specific emotions: loss tends to evoke depression, while threat tends to evoke anxiety (Aldwin, 1994; Brown & Harris, 1989). The intensity of the stress changes during the course of several consecutive unsuccessful treatments. The stress of the first cycle is most closely related to the threat of the unknown nature of the treatment, while the stress of the third (and usually last) cycle is more closely related to the threat of definitive infertility (Thiering et al., 1993). When developing interventions for managing stress that accompanies IVF/ICSI treatment, it is important not to confuse the different emotional aspects of the consecutive treatment cycles.

Some studies on the emotional aspects of IVF/ICSI treatment revealed that the women who entered an IVF program had higher state and trait anxiety scores than normal groups (Slade et al., 1997; Visser et al., 1994). Other studies, however, reported the opposite: higher depression scores among IVF women in comparison to normal group scores (Demyttenaere et al., 1998; Thiering et al., 1993).

Thiering et al. (1993) reported that stress before the start of an IVF cycle and the treatment result were related to depression, while Stoleru et al. (1999) reported a relationship to anxiety. However, Visser et al. (1994) and Slade et al. (1997) could not confirm these findings. This may have been due to a lack of differentiation between the first and following treatment cycles (Visser et al., 1994) or to the small power of the study (Slade et al., 1997). Demyttenaere et al. (1998) showed a relationship between higher levels of depression and lower pregnancy rates after IVF among women who were themselves the cause of the infertility problem, and they found the opposite to be true among women whose male partner was the cause

of the problem. Accordingly, they were unable to find a relationship between depression and IVF treatment success rate in the total group.

Most studies that examined emotional response to unsuccessful treatment revealed higher levels of depression after than before treatment. Visser et al. (1994), however, did not find any differences in emotional response between the women who became pregnant and those who did not. There is a lack of information about the emotional response of women who become pregnant after IVF/ICSI treatment, compared to those who do not. It is possible that the higher levels of depression reported among non-pregnant women after treatment are also present among pregnant women. In that case, depression would not be due to a chronic stressor resulting from the threat of infertility, but to the stressful event of the treatment.

In addition to studies on emotional response to IVF/ICSI treatment, the effect of treatment on marital satisfaction has been frequently investigated. These studies reveal that IVF treatment had neither a negative (Leiblum et al., 1998) nor positive impact (Slade et al., 1997) on marital satisfaction. However, there is a lack of information about the impact of the first cycle on marital satisfaction in comparison to the impact of subsequent cycles.

This means that there is no unequivocal information available about emotional status prior to treatment and after the first cycle of IVF/ICSI, despite the fact that many studies have been conducted on emotional aspects of IVF. Consequently, this study focussed on emotional response to the first cycle of IVF or ICSI. We compared pretreatment stress levels to stress levels after the first cycle among women who underwent their first IVF/ICSI cycle; data was obtained from the women who became pregnant and from those who did not.

In addition, we studied whether there were differences in emotional status before and after IVF or ICSI. The long term effects of ICSI are still unknown, but this treatment could result in more distress than IVF. Differences in emotional aspects related to IVF and ICSI have been investigated among men. Boivin et al. (1998) reported marginally more distress during treatment in men involved in ICSI than those involved in IVF. The retrospective study by Beutel et al. (1998) revealed more additional stress in men involved in ICSI than in IVF.

We addressed the following research questions:

1. To what extent do women entering their first IVF/ICSI treatment differ from normal groups with respect to anxiety, depression, mood, marital and sexual satisfaction?
2. What is the emotional response to the first IVF/ICSI cycle? Are there differences between the women who become pregnant and those who do not? Are there differences between IVF and ICSI?
3. What is the effect of the first IVF/ICSI cycle on marital and sexual satisfaction? Are there differences between women who become pregnant and those who do not? Are there differences between IVF and ICSI?

## **Materials and methods**

### *Design*

Data was collected with the first questionnaire before the start of medication, three to ten days before the beginning of the first cycle of IVF/ICSI ( $T_1$ ). The second questionnaire was completed three to four weeks following the pregnancy test given after the first cycle ( $T_2$ ) and, in the event of pregnancy, after the first transvaginal ultrasound. Emotional status, marital satisfaction and demographic and gynaecological background characteristics were assessed at  $T_1$ . Measurements of emotional status and marital satisfaction were repeated at  $T_2$ .

### *Procedure*

Women were asked to participate in the study during the intake interview prior to their first cycle of IVF/ICSI treatment. A long protocol with Decapeptyl® (Ferring, Hoofddorp, the Netherlands) and Puregon® (Organon, Oss, the Netherlands) was used to generate ovarian stimulation. After obtaining written informed consent, the first questionnaire was mailed to the women at home. Participants were asked to fill out the questionnaire before starting medication and return it to the hospital in a postpaid envelope. Four weeks after the pregnancy test, a second questionnaire was mailed to the women.

### *Participants*

Participants were recruited at two hospitals, a university hospital (hospital-U) and a regional hospital (hospital-R). These hospitals are located in a

moderately large city in the Netherlands. All the women treated by the Fertility Department at both hospitals for their first cycle of IVF/ICSI were invited to take part in the study. The exclusion criterion was insufficient fluency in the Dutch language. In 1999, 250 couples went to these clinics, 217 in hospital-U and 33 in hospital-R. Couples were informed about the study during the intake interview. Reasons for nonparticipation were a lack of time for completing the questionnaires (15 women), emotional stress resulting from the treatment or subject of the study (7 women), and participation in another study (4 women). In four cases, the reason for nonparticipation was unknown. Thirteen women were excluded due to insufficient fluency in the Dutch language. A total of 207 women took part in the study.

### *Measures*

Emotional status was defined in terms of state anxiety, depression and mood. To measure these three aspects of emotional status, we used three standardized questionnaires, validated for the Dutch population. Anxiety was measured with the State and Trait Anxiety Inventory (STAI; Spielberger, 1983), Dutch translation by Van der Ploeg et al. (1980). In this study, we only measured state anxiety. The state anxiety scale of the STAI consists of 20 items that measure current feelings of anxiety. Each item is rated on a 4-point intensity scale. Scores range from 20 (low anxiety) to 80 (high anxiety).

The Beck Depression Index (BDI; Beck et al., 1976) is widely used to measure clinical forms of depression and consists of 22 items. Respondents were asked to select the item that best matched the way he or she had felt in the past seven days. Beck's scale has high reliability and good validity. The Beck Depression Inventory for Primary Care (BDI-PC; Beck et al., 1997) was used to counter the risk of confounding between the vital aspects in many BDI items and early signs of pregnancy, such as fatigue and loss of appetite (Heineman et al. 2000; Holcomb et al. 1996). The BDI-PC consists of seven items out of the total BDI scale. It measures the cognitive/affective aspects of depression and omits any items that concern the vital aspect. In our sample, the BDI-PC showed satisfactory reliability (Cronbach's  $\alpha=0.79$ ). We also calculated a vital depression score by adding the scores on the three vital items of the BDI that are usually related to early signs of pregnancy - fatigue, loss of appetite and disturbed sleeping habits. The multivariate analysis of variance was

restricted to the BDI-PC score, because we were interested in the effect of IVF/ICSI on depression levels, distinguished from physical characteristics of early pregnancy. In the descriptive analysis, we used all three BDI scales (total, primary care and vital) to indicate the different courses of the three depression scales.

Mood was measured with the Profile of Mood Scale (POMS; McNair et al., 1971, Dutch translation by Wald & Mellenbergh, 1990). It consists of an inventory for measuring five types of moods: sadness, fatigue, irritation, tension and vigour. A total negative mood score was obtained by adding together the three negative mood scales of sadness, irritation and tension. The negative scale 'fatigue' was not used, because it could be contaminated by normal characteristics of pregnancy. Positive mood was measured with the 'vigour' scale. Accordingly, the POMS-negative score is an indication of the severity of negative mood: higher scores indicate of higher levels of negative mood. The POMS-positive score is an indication of positive mood or vigour, higher scores indicating higher levels of positive mood.

Marital satisfaction was measured with the Maudsley Marital Questionnaire (MMQ; Arrindell et al., 1983). This inventory consists of 20 items. Respondents were asked to rate their satisfaction on a 9-point scale. Higher scores indicate greater dissatisfaction. The scores on the 20 items can be reduced to three scale scores: general marital satisfaction, sexual satisfaction and general life satisfaction. In view of the aims of this study, only general marital and sexual satisfaction scales were used.

### *Statistical analyses*

Differences in emotional status and marital satisfaction prior to and after the first IVF/ICSI cycle and their relation to the result of the treatment were measured with Multivariate Analyses of Variance (MANOVAs). We examined main and interaction effects of the within-subject time-of-measurement factor (before or after the first IVF cycle) and the between-subject pregnancy factor for emotional status and marital satisfaction. Additional analyses were carried out to measure the effects of the between-subject 'type of treatment' factor (IVF versus ICSI) for emotional status and marital satisfaction.

Because of high levels of kurtosis and skewness on the three BDI scales and the POMS-negative mood scale, as an indication of no normal distribution, square root levels were used in the t-tests and MANOVAs

(Tabachnick & Fidell, 1996). These square root values were normally distributed.

## Results

In 1999, 174 women, consecutive patients from the fertility department at hospital 1 and 33 women from the fertility IVF department at hospital 2 agreed to complete the first questionnaire several days before the start of their first cycle of treatment. T-tests for independent samples did not reveal any differences in outcomes, gynaecological or demographic parameters between the women from both hospitals. At T<sub>2</sub>, four weeks after their pregnancy test, 66% (N=127) of these women also completed a second questionnaire. Sixteen percent of the women (N=33) who did not complete the second questionnaire had not finished their first cycle of treatment at the time when the data was collected. Another 23% (N=47) dropped out of the study: eight women because of the emotional stress of some of the questions, 18 women because they did not have time to complete the questionnaire and 12 women due to the emotional stress of the treatment. For nine women the reason for drop-out was unknown. Drop-out rates were the same in the non-pregnant and pregnant groups (Chi square=0.18; p=0.40). In addition, the dropouts did not differ significantly from participants in terms of scores for depression and negative mood. State anxiety levels, however, did differ. A t-test of the differences in mean scores revealed that dropouts had higher scores on state anxiety than those who continued to participate (t=-2.2; p=0.03).

After one treatment, 26% of the women became pregnant. A male factor was the most frequent cause of the fertility problems. Fertility problems could be categorized as follows: male factor 42%, female factor 25%, both male and female factor 9%, and idiopathic 24%. Almost a quarter of the couples (24%) already had one or more children of their own, which means that 76% of the couples were not parents at that time. Sixty-two percent of the couples underwent IVF and 38% underwent ICSI. Twelve and a half percent of the women had previously received IVF or ICSI treatment. In 9% of the cases, treatment had been successful, and these women already delivered at least one child. The mean age of the total group of women was 33.4 (+/- 3.7) years and the mean duration of fertility problems was 3.7 years (+/- 2.0).



**Table 1.** Women's pretreatment mean scores and SDs on emotional and marital variables: (prospective) pregnant and non-pregnant women

	T <sub>1</sub>	
	Pregnant (N= 59)	Non-pregnant (N=148)
STAI, state	35.6 ± 8.3	38.0 ±10.9*
BDI, total	4.1 ± 3.6	6.4 ± 5.8**
BDI-PC	0.7 ± 1.4	1.3 ± 2.1**
BDI, vital	0.9 ± 1.0	1.1 ± 1.1
POMS-negative	11.7 ±12.0	12.6 ±12.5
POMS-positive	11.9 ± 4.3	11.5 ± 4.3
Marital satisfaction <sup>a</sup>	18.6 ± 8.5	17.3 ± 8.7
Sexual satisfaction <sup>a</sup>	10.8 ± 5.6	11.0 ± 7.0

<sup>a</sup> higher scores means more dissatisfaction

\* a trend towards a difference between pregnant and non-pregnant women:  
t-test:  $p < 0.10$

\*\* difference between pregnant and non-pregnant women: t-test:  $p < 0.05$

#### *Emotional status before the start of the first cycle*

Table 1 presents mean scores for emotional factors among the women who became pregnant after the first cycle and those who did not. There was no deviation in state anxiety scores measured with the STAI from those of an age-matched and sex-matched normal group. The scores on the BDI could not be measured against a Dutch matched sample, because there was no normal group. However, according to the classification by Beck et al. (1997), a BDI-PC cutoff score of four and above correctly classifies 82% of patients with a major depressive disorder, according to the DSM-IV. In our sample, 8% of the women had a score of four or more on the BDI-PC. Comparison of the patients' scores and normal scores for the total scale and the subscales of the POMS did not reveal any deviation from those of a sex-matched normal group.

Before the start of the first cycle, the scores for the IVF and ICSI women on marital and sexual satisfaction did not differ from those of the normal group (Arrindell et al., 1983).

Comparisons of mean scores (see Table 1) revealed that at T<sub>1</sub>, the women who became pregnant had lower levels of depression than those who did not (BDI-total;  $t = -2.29$ ). More specifically, they showed lower scores on the

cognitive/affective aspects of depression (BDI-PC;  $t=-2.35$ ). Differences in depression scores between these groups of women also lead to differences in the amount of women who score above the 4-point cutoff for clinically relevant types of depression. Ten percent of the women who did not become pregnant scored in the domain of clinically relevant aspects of depression, compared to 5% of the women who did become pregnant. We did not find significant differences between these groups of women for other emotional factors. However, it might be possible to identify a trend towards higher levels of state anxiety among women who did not become pregnant, compared to those who became pregnant (STAI;  $t=-1.61$ ). In addition, pregnant and non-pregnant women did not differ on gynaecological variables that seem related to the success rate of IVF/ICSI, such as age, previous pregnancies, children and duration of fertility problems (data not presented).

**Table 2.** Women's mean scores on emotional and marital variables: (prospective) pregnant and non-pregnant women, pretreatment and posttreatment

	T <sub>1</sub>		T <sub>2</sub>	
	Pregnant (N=39)	Non- pregnant (N=88)	Pregnant (N=39)	Non- pregnant (N=88)
State anxiety	34.8± 7.3	36.7±10.4	35.3±10.8	39.2±10.6
Depression	4.4± 3.5	5.9± 5.0	6.1± 4.1	7.5± 6.8
Depression, PC	0.8± 1.2	1.1± 1.9	0.9± 1.3	1.8± 2.4
Depression, vital	0.9± 1.0	1.1± 1.1	1.8± 1.1	1.1± 1.1
Negative mood	11.1±10.1	12.2±11.4	8.8± 9.4	16.2±14.8
Positive mood	12.0± 3.8	12.0± 4.5	9.3± 4.0	10.2± 4.6
Marital dissatisfaction	18.6± 8.5	17.3± 8.7	20.2± 6.8	17.3± 9.8
Sexual dissatisfaction	10.8± 5.6	11.0± 7.0	13.7± 5.5	11.7± 7.9

#### *Emotional response to treatment*

Table 2 shows the mean scores for state anxiety, depression, depression PC, vital aspects of depression, negative and positive mood as well as marital and sexual satisfaction for women who completed questionnaires at T<sub>1</sub> and T<sub>2</sub> (N=127).

**Table 3.** Multivariate and univariate analysis of variance in emotional status, F-ratio for time (T), pregnancy (P) and Time x pregnancy (T x P) (N=127)

	<b>Within Ss Time (T)</b>	<b>Between Ss Pregnancy (P)</b>	<b>Interaction effect (T x P)</b>
Main effects	9.00	1.79	4.12
Univariate effects			
State Anxiety	1.72	2.03	0.30
Depression, PC	12.18	2.60	2.71
Negative mood	0.01	2.70	0.99**
Positive mood	20.03**	0.38	0.94

\*\* p<0.01

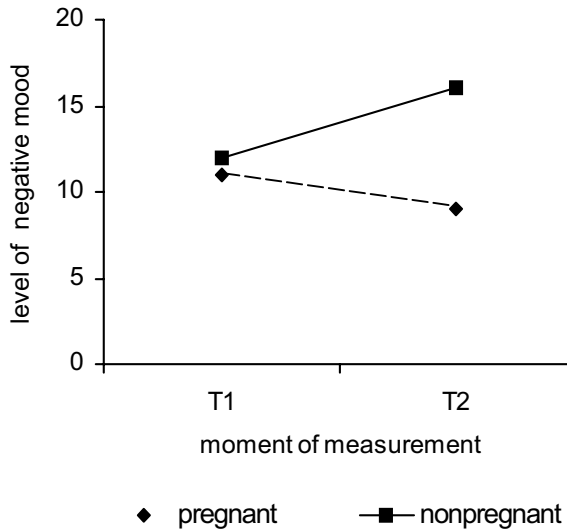
After the first treatment cycle, the amount of women who scored above the 4-point cutoff for clinically relevant types of depression, increased by 60% in the non-pregnant group and remained stable in the pregnant group (data not presented).

MANOVAs were carried out to determine the effects of time (within-subjects effect: T<sub>1</sub>, prior to treatment, and T<sub>2</sub>, four weeks after the pregnancy test) on state anxiety, cognitive and affective aspects of depression and positive and negative mood, as well as the effect of the result of treatment (between-subjects effect: pregnant and non-pregnant). We also examined the extent to which the effect of time differed with respect to the result of treatment (interaction effect). The results are presented in Table 3.

Examination of Table 3 reveals that there is a significant emotional response to the first IVF/ICSI treatment which differs for pregnant and non-pregnant women. Analysis of univariate effects revealed an effect of time on depression PC and positive mood. An interaction effect between treatment and pregnancy could be identified in negative mood (POMS). In Figure 1, the mean negative mood scores are graphically presented.

After treatment, non-pregnant women showed an increase in negative mood, while pregnant women showed a decrease.

In addition, MANOVAs were carried out for marital and sexual satisfaction as dependent variables, time of measurement as a within-subject variable and result of treatment as a between-subject factor (see Table 4).



**Figure 1.** Negative mood pre-(T<sub>1</sub>) and post-(T<sub>2</sub>) first IVF/ICSI treatment cycle, differences between pregnant and non-pregnant women

Table 4 indicates that dissatisfaction with the partner relationship changed in both pregnant and non-pregnant women after the first treatment cycle. This effect is explained by an increase in sexual dissatisfaction. The mean scores in Table 2 show that higher levels of sexual dissatisfaction occurred both among women whose treatment succeeded and those whose treatment did not, compared to dissatisfaction prior to treatment.

**Table 4.** Multivariate and univariate analysis of variance in marital and sexual dissatisfaction, F-ratio's for time (T), pregnancy (P) and Time x pregnancy (T x P) (N=127)

	Within Ss Time (T)	Between Ss Pregnancy (P)	Interaction effect (T x P)
Main effects	5.50**	2.45	0.30
Univariate effects			
Marital dissatisfaction	0.88	4.26	<0.01
Sexual dissatisfaction	10.05**	3.98*	0.40

\* p<0.05 ; \*\* p<0.01

*Effect of the type of the treatment*

Additional MANOVAs were carried out to determine the extent to which the type of treatment could explain differences in emotional variables. They indicated that emotional response to IVF treatment did not differ significantly from emotional response to ICSI treatment (Main effect of the type of treatment:  $F(2,125)=1.68$ ;  $p=0.16$ ; interaction effect of the type of treatment x pregnancy:  $F(2,125)=2.08$ ;  $p=0.09$ ).

In addition, the type of the treatment did not explain variance in marital and sexual satisfaction (Main effect of type of treatment:  $F(2,125)=0.05$ ;  $p=0.95$ ; interaction effect of the type of treatment x pregnancy:  $F(2,125)=0.18$ ;  $p=0.84$ ).

**Discussion**

The women in this sample did not differ from those in normal groups in terms of levels of anxiety, depression, mood and marital satisfaction. This is only partly in agreement with other studies. Some studies reported higher levels of distress in women beginning IVF or ICSI treatment, while others did not detect any differences. This lack of agreement can be explained by examining different points in the course of the treatment where data was collected. Some studies (Thiering et al., 1993) gathered data several months before the start of treatment, while others (Slade et al., 1997; Visser et al., 1994) did so just before or just after the start of medication. Distress levels can be expected to be higher just before the start of a first IVF/ICSI treatment than several months earlier. However, the stress that accompanied threatening infertility may be tempered by couples' high expectations and optimism about their chances of success of their first treatment (Johnston et al. 1987).

Another explanation of the relatively low levels of anxiety is a possible selective attrition of very anxious women. Inclusion of these women in the sample would probably increase the anxiety levels of the whole group.

Even in pretreatment, women who became pregnant reported lower levels of depression than those who did not. In addition, a tendency could be identified towards lower anxiety scores among women whose first treatment succeeds, compared to women whose first treatment does not. These pretreatment differences in emotional status became more apparent after the first treatment. In pregnant women, scores on negative mood decreased; in non-pregnant women, these scores increased considerably.

However, successful treatment did not produce lower levels of depression. Depression scores in women whose treatment succeeded did not decrease; they even increased slightly, despite the fact that the vital aspects of depression were left out of the analysis. This may be due to the fact that the initial success of the treatment is still fragile. The same explanation can be given for the lack of an expected increase in positive mood among pregnant women. Fear of miscarriage may still be present so soon after the first ultrasound. However, the POMS positive mood scale consists of items having elements of activity and energy. These aspects might be related to signs of early pregnancy, as shown by the enhanced levels of the vital aspects of depression in pregnant women. This data makes clear that scores on inventories measuring depression and mood in a medical setting must be interpreted carefully due to expected confounding between vital aspects of depression and mood and physical aspects of a medical status, in this case pregnancy.

The lack of significant differences between pregnant and non-pregnant women in terms of anxiety scores may be exaggerated. We have already mentioned most women's unrealistic expectations for the chances of their first treatment success. Anxiety may be more apparent before another treatment, after women have already gone through the possibility of failure. Another reason for possibly exaggerated anxiety scores is related to dropouts. We consider this point in more detail in the last part of the discussion.

In contrast to the results of other studies, we could not find any relationship between the cause of fertility problems and emotional response to IVF/ICSI. This can be explained by the enhanced possibilities for couples with a male factor as the cause of the fertility problem. ICSI treatment has represented a great improvement of treatment possibilities for men with fertility problems. This can also explain why the distribution of different causes of fertility problems varies in our sample compared to that in other samples. ICSI treatment has only recently been possible on such a large scale.

The findings of this study indicate that the majority of the women did not develop severe levels of distress after an unsuccessful IVF/ICSI treatment cycle. However, the small group of women that did suffer from depressive symptoms increased significantly. Longitudinal studies of the implications of enhanced levels of depressive symptoms have revealed that people with depressive symptoms were 4.4 times more likely to develop an initial onset

of a major depressive disorder after one year (Howarth et al., 1994) in comparison to those who did not have symptoms of depression. When we take into account that most of the non-pregnant women will at least face the stressful event of another IVF/ICSI treatment within a year after a single IVF or ICSI treatment cycle, the risk of development of clinically relevant types of depression is considerable.

Anxiety did not increase after an unsuccessful treatment cycle. The difference in the scores on the affective and cognitive components of depression between pregnant and non-pregnant women after the first unsuccessful treatment cycle seems due to the chronic stress of the threat of infertility. At the time of the second measurements about four weeks after the pregnancy test, the stressful event of the IVF or ICSI treatment itself no longer seems to play a role.

One of the study's limitations is that we were unable to gather information on emotional and marital factors in the group of women who from the beginning refused to participate in the study. This group of non participants may on average be more anxious than women who participated in the study. This may be confirmed by the fact that stress was an important reason for nonparticipation.

Another problem is the selective drop out of relatively highly anxious patients. Without this drop out group, we have already noticed a trend towards increased levels of anxiety after the first treatment. It is possible that the addition of information on these women could make the anxiety results more striking. It will be difficult, however, to further decrease the drop-out rate. Comparable studies on stress and IVF that monitored women during the treatment process reported even higher drop-out rates (Slade et al., 1997; Visser et al., 1994).

In a follow-up study, we intend to examine whether the relationship between depression and pregnancy rates after the first cycle of IVF/ICSI can be explained by scores of the small, highly depressed group of women. If so, stress management strategies could possibly be focussed on this group of women. In addition, examining the effect of stress-reducing interventions for this group of women on the success rate of IVF/ICSI treatment would be worthwhile. This study indicates that stress-reducing interventions may have to focus on depression management.

To sum up, this study has indicated that even in pretreatment, there are differences in emotional status between women who become pregnant and women who do not. After the first unsuccessful treatment cycle, these

differences became more apparent. While most women prefer to start a second treatment cycle soon after the first, the increased levels of distress determine emotional status before the start of the second treatment. These increased levels of distress could be a less favourable starting point for the next treatment cycle and may represent a risk to the development of clinically relevant types of depression. If this trend continues after another unsuccessful treatment cycle, the importance of stress management programs for IVF/ICSI patients will increase in the course of several treatment cycles.





## Chapter 3

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Emotional impact of the IVF or ICSI treatment:  
increased anxiety and depression  
following an unsuccessful first treatment cycle\*

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\* Translated from Dutch into English and slightly adapted



## **EMOTIONAL IMPACT OF THE IVF OR ICSI TREATMENT: INCREASED ANXIETY AND DEPRESSION FOLLOWING AN UNSUCCESSFUL FIRST TREATMENT CYCLE**

### **Abstract**

The aim of the study was to determine the emotional stress of the first IVF or ICSI treatment cycle, the impact of treatment on the marital relationship, and the course of treatment after both successful and unsuccessful cycles. A descriptive longitudinal design was used with repeated measures prior and subsequent to the first treatment cycle. Two hundred and fifty-nine women and 217 men completed questionnaires on anxiety, depression and marital relationship (Spielberger State Trait Anxiety Inventory [STAI], Beck Depression Inventory for Primary Care [BDI-PC] and Maudsley Marital Questionnaire [MMQ], respectively) as well as their plans for further treatment. The results indicated that after their first unsuccessful treatment cycle, women showed a significant increase in anxiety and depression in comparison to pretreatment, while men showed a rise in depression. Anxiety and depression in this group of couples did not increase after successful treatment. About 20% of the women scored within the range of sub clinically relevant depression after their first unsuccessful treatment cycle. Dissatisfaction with their sexual relationship increased for both men and women, regardless of treatment results. Two per cent of the couples had no intention of undergoing subsequent treatment if the first cycle was unsuccessful. In fact, none of these couples underwent another cycle. Ultimately, 18% of the couples refrained from further treatment after an unsuccessful first cycle. In conclusion, after an unsuccessful treatment cycle, couples scored higher in depression and one out of eight women had a clinically relevant form of depression. More than one out of six couples decided against further treatment after an unsuccessful first cycle.

### **Introduction**

Medical developments in reproductive medicine are rapidly advancing and they raise many ethical, medical, political and psychological issues (De Wert, 1999; De Wert & De Beaufort, 1991). This was made apparent during the 'Night of Reproduction' organized by the Rathenau Institute (De Joode, 2001; Kirijczyk et al., 2001). One of the publications presented at this festival describes the significance of in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) treatments for patients from an

anthropological and philosophical perspective (Kirijczyk et al., 2001). This publication emphasizes the emotional stress of treatment, the strain on the marital relationship and the difficulties of a premature discontinuation of the treatment.

It is striking that the psychological aspects of IVF and ICSI treatment have so far received little attention in the Netherlands. The treatments are physically stressful, time consuming and not without medical risks (Evers & te Velde, 1999). However, couples experience the emotional rather than the physical aspects of treatment as most stressful (Hammer-Burns & Covington, 2000). This particularly applies to the period they have to wait for the results (Boivin & Takefman, 1995; Berg & Wilson, 1991). International studies are geared more to the psychological features of IVF and ICSI treatments (Slade et al., 1997; Boivin et al., 1995; Visser et al., 1994). Yet, there are very few longitudinal studies that focus on differences in emotional responses between men and women subsequent to successful and unsuccessful treatments. In addition, very little is known about the number of couples that discontinue treatment after their first unsuccessful treatment cycle.

To gain more insight into the emotional stress of IVF and ICSI treatments, the University Medical Centre (UMC) St. Radboud in Nijmegen, the Netherlands, studied in 1999 and 2000, couples eligible for their first treatment cycle. Provisional results based on some of the women admitted during this period showed an increase in depression after unsuccessful treatment (Verhaak et al., 2001). In this article, we describe the emotional stress of the first treatment cycle for both men and women. To this end, we examine the courses of anxiety, depression and satisfaction with marital relationships from the period just prior and immediately subsequent to the first treatment cycle. We also examine couples' deciding whether or not to discontinue treatment before completion. This article focuses on the following issues:

- What are the emotional responses to the first unsuccessful IVF and ICSI treatment cycles? To what extent do men's and women's responses differ after successful and unsuccessful treatment?
- What is the effect of treatment on marital and sexual relationships, and to what extent does this differ between men and women after successful and unsuccessful treatment?
- How many couples consider discontinuing treatment after the first cycle, and how many couples actually do so?

## Patients and Method

*Patients and Procedure.* Couples who applied for their first IVF or ICSI treatment cycle in the period from January 1999 - December 2000 at UMC St. Radboud were invited to take part in the study. Four hundred and fifty couples applied during this period, 363 of which (81%) were willing to take part and completed the first set of questionnaires. The IVF and ICS treatments comprised a long protocol with tryptorelin, follitropin and choriogonadotrophin. After the couples had provided written informed consent to participate in the study, a questionnaire was mailed to them, before the start of treatment, prior to the start of treatment with a gonadotropin-releasing hormone agonist ( $T_1$  period), and four weeks after the pregnancy test ( $T_2$  period). A maximum of two embryos were transferred during each treatment cycle.

The study was approved by the UMC St. Radboud Human Medical Research and Ethics Committee.

*Measures.* Dependent variables included state anxiety, measured with the 'Spielberger State Trait Anxiety Inventory' (STAI; Spielberger, 1983), depression measured with the 'Beck Depression Inventory for Primary Care' (BDI-PC; Beck et al., 1997), and marital satisfaction measured with the 'Maudsley Marital Questionnaire' (MMQ; Arrindell, 1983). These instruments have been found reliable and valid in national and international studies (van der Ploeg et al., 2000; Howarth et al., 1994; Bouman et al., 1985).

Couples were also asked to indicate whether they would consider undergoing another IVF or ICSI treatment cycle in the event of unsuccessful treatment. At the conclusion of their first unsuccessful treatment cycle, men were also asked whether they wanted to undergo another cycle, and how soon they would prefer to do so.

*Statistical methods.* Descriptive analyses were used to answer the study questions. MANOVA for paired observations were performed to examine differences in stress between the times prior and subsequent to the first treatment cycle.

## Results

*Background data.* Two hundred and fifty-nine women (response of 71% of 363) and 217 of their partners both returned fully completed first and second questionnaires. Average age for the 259 women was 34.1 years

(range=21-43; SD=3.9) and 36.3 for the 217 men (range=26-54; SD=4.8). The average duration of infertility was 3.5 years (range=1-13). Women were the cause of the infertility problems in 23% of the cases, men in 40% of the cases, both men and women in 8% of the cases, and the cause was unknown in 29% of the cases. Sixty-nine of the 259 women who returned the second questionnaire were pregnant (27%). The women who dropped out of the study (those who completed a first but no second set of questionnaires) had a lower percentage of pregnant women (between measurement points) than the group of respondents ( $z=-2.09$ ;  $p=0.04$ ), which means that the attrition among non-pregnant women was greater than among pregnant women. There were no differences in pretreatment scores for anxiety, depression, age or educational level between the dropout and respondents groups.

**Table 1.** State anxiety, depression, dissatisfaction with the marital and sexual relationships for both women and men prior ( $T_1$ ) and subsequent to ( $T_2$ ) their first IVF or ICSI treatment cycle, expressed as a score (SD)<sup>1</sup>

Women	successful (n = 69)		unsuccessful (n = 190)	
	$T_1$	$T_2$	$T_1$	$T_2$
state anxiety	35.7 (9.5)	34.1 (9.0)	36.6 (10.4)	39.1 (11.4)
depression	1.3 (1.8)	0.6 (1.0)	1.4 (1.9)	2.1 (2.2)
marital relationship	9.7 (6.0)	9.8 (7.4)	10.4 (7.4)	10.9 (7.8)
sexual relationship	8.1 (5.6)	10.8 (7.5)	7.9 (5.9)	8.5 (5.8)

Men	successful (n = 62)		unsuccessful (n = 155)	
	$T_1$	$T_2$	$T_1$	$T_2$
state anxiety	32.4 (7.6)	32.5 (7.1)	33.7 (8.7)	35.2 (9.1)
depression	0.7 (1.0)	0.5 (0.9)	0.9 (1.5)	1.0 (1.5)
marital relationship	8.1 (5.2)	7.9 (5.0)	8.2 (5.8)	8.4 (6.7)
sexual relationship	6.8 (6.3)	11.5 (7.7)	6.3 (5.4)	7.1 (5.8)

<sup>1</sup> IVF = in vitro fertilization; ICSI = intracytoplasmic sperm injection  
Higher scores signify greater anxiety, depression and dissatisfaction with the marital or sexual relationships

*Anxiety, depression and dissatisfaction.* Table 1 gives the scores for women and men on anxiety, depression and dissatisfaction with their

marital and sexual relationship prior and subsequent to their first treatment cycle.

The results of the MANOVAs for women revealed a significant treatment outcome and interaction effect for anxiety [treatment outcome  $F(2,257)=4.81$ ;  $p=0.03$ ]; time x treatment outcome  $F(2,257)=10.63$ ;  $p<0.01$ ] and depression [treatment outcome  $F(2,257)=10.53$ ;  $p<0.01$ ]; time x treatment outcome  $F(2,257)=25.87$ ;  $p<0.01$ ]. Post hoc t-tests revealed a significant increase in anxiety ( $t=-4.98$ ;  $p<0.01$ ) and depression ( $t=-3.47$ ;  $p<0.01$ ) in women who did not become pregnant, pregnant women showed a significant decrease in depression ( $t=3.25$ ;  $p<0.01$ ). The results of men showed no significant time, outcome or interaction effect. Prior to treatment, 11% of the women and 5% of the men showed sub clinically relevant forms of depression. After the first treatment cycle, this percentage rose among women to 16% (3% after successful treatment and 21% after unsuccessful treatment) and remained about the same among men (2% and 7% after successful and unsuccessful treatment cycles, respectively). Satisfaction with the marital relationship did not change between measurement points prior and subsequent to treatment, regardless of the result. Dissatisfaction with their sexual relationship did increase, however, for both men and women [the following applied to the time effect for women:  $F(2,257)=24.02$ ;  $p<0.01$ , and for men:  $F(2,215)=46.95$ ;  $p<0.01$ ]. The increase in dissatisfaction was greatest after successful treatment [the following applied to the interaction effect of time and the result of treatment for women:  $F(2,257)=9.39$ ;  $p=0.02$ , and for men:  $F(1,215)=22.61$ ;  $p<0.01$ ].

*Deciding against further treatment.* Prior to the first treatment, 313 of the original 380 couples (82%) indicated certain or nearly certain willingness to attempt another treatment cycle if the first was unsuccessful. Eight women (2%) said they would not or probably would not want to undergo another treatment cycle. The other women were uncertain. None of the women who would not or probably would not want to undergo another treatment cycle if the first failed started a second treatment cycle, despite the fact that four of them had not become pregnant after the first cycle. Ultimately, 53 women (18%) did not undergo another treatment cycle after their first unsuccessful cycle. Post hoc analyses showed that the group of women who stopped after the first treatment cycle had scored higher on anxiety ( $t=3.1$ ;  $p<0.05$ ) and depression ( $t=3.1$ ;  $p<0.05$ ) than the other women. They did not differ in



terms of satisfaction with their marital relationship ( $t = -0.4$ ;  $p=0.68$ ) or their sexual relationship ( $t=-0.6$ ;  $p=0.96$ ).

Most of the women (85%) and men (87%) preferred to start the next treatment cycle within three months after their first unsuccessful treatment. One percent of the women and one percent of the men said they wanted to wait more than 6 months.

### **Discussion**

After unsuccessful IVF or ICSI treatment both women and men showed higher levels of depression than at the start of treatment. For women, this confirms previously published provisional results (Verhaak et al., 2001). Women also displayed an increase in anxiety, but the rise in depression was the greatest, which indicates that unsuccessful treatment tends to result more in feelings of loss than of threat. Approximately one out of five women and one out of thirteen men scored within the realm of sub clinically relevant forms of depression after an unsuccessful first treatment cycle. This indicates that these women run an increased risk of developing serious emotional problems (Howarth et al., 1994). This group requires attention and could benefit from additional psychological interventions.

Our results could be affected by the selective dropout of couples who experienced an unsuccessful first treatment cycle. Although their depression scores do not differ from the other couples' at the start of treatment, it is possible that specifically this group would have shown a sharper increase in depression. In addition, it should be born in mind that depression could increase after undergoing more than one unsuccessful treatment cycle (Slade et al., 1997).

Both men and women reported greater dissatisfaction with their sexual relationship after successful treatment than couples after unsuccessful treatment. This is in line with the literature, which reports a decreased desire for sexual contact in pregnant women (Brancroft, 1989).

Prior to starting the first treatment cycle, the great majority of the couples said they would definitely or probably want to undergo another cycle if the first proved unsuccessful; two percent of the couples thought they would not or probably would not want to attempt another cycle if the first was unsuccessful. None of these couples underwent another cycle. A total of 18% of the couples decided against further treatment after their first unsuccessful cycle, either with or without advice from their physician. Post

hoc analyses indicate that women who decided against further treatment showed greater anxiety and depression at the start of treatment than women who became pregnant or continued treatment. This suggests that psychological factors might play a role in the decision to discontinue treatment. Further research will have to clarify this.



## **Part 2**

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Factors that contribute  
to the short term course of emotional response



## Chapter 4

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Neuroticism, preattentive and attentional biases towards  
threat, and anxiety before and after a severe stressor:  
a prospective study

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**NEUROTICISM, PREATTENTIVE AND ATTENTIONAL BIASES TOWARDS THREAT, AND ANXIETY BEFORE AND AFTER A SEVERE STRESSOR: A PROSPECTIVE STUDY****Abstract**

The present study was designed to prospectively investigate the role of neuroticism, trait anxiety and attentional biases towards threat in the development of anxiety after an unsuccessful IVF or ICSI treatment. A subliminal and supraliminal Stroop task was administered to 49 women entering IVF or ICSI treatment as well as self-report measures of neuroticism, trait anxiety and state anxiety. The assessment of state anxiety was repeated after unsuccessful treatment. Results of concurrent analyses have indicated that there was no relationship between Stroop factors and state anxiety. As hypothesised, prospective analyses showed a significant effect for neuroticism and Stroop interference on anxiety response to unsuccessful IVF or ICSI treatment. This effect was only apparent for interference on stressor-related words and not for words related to general threats. The effect of subliminal Stroop interference was more pronounced in a subsample of women showing an increase in anxiety as a result of unsuccessful treatment. It can be concluded that, in addition to neuroticism, subliminal Stroop interference is another predictor for emotional response to an aversive stressor, such as unsuccessful IVF or ICSI treatment.

**Introduction**

Stress vulnerability models differ in their attention to factors supposed to be the main predictors of the development of anxiety disorders. Models of personality dimensions stress the importance of neuroticism and trait anxiety, whereas cognitive models stress the importance of information processing. Until now, studies have mainly focussed on one of these two models, as a result of which relatively little attention has been paid to the additional contribution of factors from both models in the development of anxiety disorders. Information about this would increase our understanding of how to identify which individuals are more vulnerable than others to developing anxiety. The object of the present study is to illuminate this by investigating the concurrent and prospective relationship between factors of both models and state anxiety, before and after the occurrence of an aversive stressor.



Personality theories have stressed the importance of negative affectivity and underlying constructs, such as neuroticism and trait anxiety. It is assumed that individuals vulnerable to developing anxiety disorders are characterised by enhanced sensitivity to aversive stimuli (Eysenck, 1998; Clark, Watson & Mineka; 1994; Watson & Clark, 1984; Eysenck, 1970). This enhanced sensitivity is the main characteristic of negative affectivity. Neuroticism can be defined as a general sensitivity to negative information, trait anxiety as an enhanced sensitivity to threatening information. Neuroticism and trait anxiety are generally assessed by self-report measures, like the Eysenck Personality Questionnaire (Eysenck & Eysenck, 1975) and the Spielberger Trait and State Anxiety Inventory (Spielberger, 1983).

Cognitive theories have proposed that enhanced vulnerability is explained by the selective processing of threatening information (Mogg & Bradley, 1998; Williams et al., 1997). In anxiety, selective processing is shown as an attentional bias towards threatening information. Pathological fear occurs when a fear structure is activated without further processing of threatening information (Foa & Kozak, 1986). Further processing involves incorporation of new information that is incompatible with the fear structure and results in its modification. Activation of the fear structure causes an orientation towards threat in the initial phase of information processing. This orientation towards threat seems to make information appear to be more threatening (Mogg & Bradley, 1998). Relaxed subjects are better able to entirely process threatening information, whereas this entire processing takes too much effort when subjects are under stress (Foa & Kozak, 1986). Foa and Kozak did not differentiate between preconscious and conscious activation of fear structures. Later theories, like those of Beck and Clark (1997) and Mogg and Bradley (1998), proposed that biases in the processing of threatening information take place on preattentive (preconscious) and attentional (conscious) levels.

Preattentive and attentional biases towards threatening information are most frequently identified with an emotional Stroop task. In the emotional Stroop task, subjects are asked to name the colour of a word as quickly as possible, while ignoring the meaning of the word. Colour-naming interference is positively related to the emotional valence of the word.

Attentional biases towards general threat words are most frequently identified in clinical samples (see for reviews: Mogg & Bradley, 1998; Williams et al. 1996; Mathews & MacLeod, 1994). A few studies have also

reported a preattentive bias towards threatening information in clinical samples (Lundh et al., 1999; Mogg et al., 1993<sup>a</sup>).

In non-clinical samples, there is less evidence of a relationship between anxiety and attentional biases towards threatening information. MacLeod and Ruthenford (1992) proposed that this could be due to the fact that highly anxious subjects in non-clinical samples are able to strategically override a possible processing bias for threatening information. This capacity is assumed to be lacking in patients with anxiety disorders. This might explain why an attentional bias towards threat-related words is indicated most consistently in clinical groups. However, it is possible that, while non-clinical subjects strategically override a processing bias on the supraliminal level, they are not able to do this on the subliminal level. Thus non-clinical subjects with high levels of trait anxiety could show a preattentive bias towards threat. Indeed, there is evidence for a relationship between preattentive biases towards threat and trait anxiety in non-clinical groups (Mogg et al., 1993<sup>a</sup>; MacLeod & Ruthenford, 1992), but studies on this issue have small samples, equivocal results and are based on samples with high trait anxiety.

Accordingly, in clinical samples, there seems to be support for a concurrent relationship between anxiety and preattentive and attentional biases towards threat. In non-clinical samples, however, the relationship between both of these factors has been insufficiently demonstrated. So, the question concerning the concurrent relationship between preattentive biases towards threat and anxiety in a normal sample with respect to anxiety levels remains unanswered.

Up to now, prospective studies on the relationship between preattentive and attentional biases towards threat and anxiety have been rare. A prospective design is warranted in order to exclude the possibility of a preattentive or attentional bias being a consequence of anxiety, and not being a mediating factor in the course of anxiety. MacLeod and Hagan (1992) used a quasi prospective design in a sample of 32 gynaecological patients due for a colposcopy after a positive cervical test. Based on the results of their study, they concluded that the subliminal attentional bias before the stressor was a better predictor for emotional response to that stressor than self-report measures on state and trait anxiety. Supraliminal Stroop interference was not a predictor for emotional response. This supports an assumption of possible strategic overriding in non-clinical subjects with high trait anxiety. Caution in drawing firm conclusions should

be exercised, however, because of the small sample size and the consequently limited power of their study. Until now, the prospective results of MacLeod and Hagan's study have only been partly replicated (Pury, 2002; van den Hout et al., 1995). Accordingly, the relative contribution of subliminal threat interference along with dispositional factors as assessed by self-report measures is still unclear.

The present study was carried out for two purposes, firstly to explore the concurrent relationship between neuroticism, trait and state anxiety and attentional and preattentive biases towards threat in a non-clinical sample. Secondly, to investigate the relative contributions of neuroticism, trait anxiety and Stroop interference to anxiety response to an aversive stressor. The study sample consisted of women about to start in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) treatment. Before the start of the treatment, IVF or ICSI patients showed trait and state anxiety levels comparable to sex and age-specific norm groups (Verhaak et al., 2001). The nature of the IVF/ICSI treatment provides a good opportunity to prospectively study the predictive value of neuroticism and processing biases for the development and consolidation of anxiety in a natural setting with non-clinical subjects before and after experiencing a severe stressor. The success rate of an IVF treatment is low (first cycle only about 25%), while its emotional and physical strain is considerable (for a review see: Eugster & Vingerhoets, 1999). A treatment cycle takes about six weeks, in which women first inject themselves with hormones to stimulate follicle growth. When follicles are sufficiently present, retrieval of oocytes takes place. Two days after fertilization, two embryos are replaced in the womb. A pregnancy test is performed two to three weeks after the embryo transfer. In the Netherlands, insurance companies pay for three treatment cycles. According to vulnerability models for the aetiology of clinical anxiety, an unsuccessful treatment cycle can be considered as a severe stressor able to trigger relatively high levels of anxiety in more vulnerable women.

This study was undertaken to investigate both the concurrent and the prospective relationship between self report measures of personality characteristics, state anxiety and Stroop interference. The results of studies into the concurrent relationship between these self report measures and Stroop interference revealed equivocal results, partly due to differences in characteristics of the samples of the studies. In the present study, we

explored this relationship in a non-clinical sample of women entering fertility treatment.

Theories on the processing of threatening information assume that preattentive and attentional biases towards threat is a determinant of enhanced vulnerability to developing an anxiety response as the result of a stressor (Mogg & Bradley, 1998; Williams et al., 1997). Empirical evidence has indicated that attentional biases towards threat in non-clinical samples seem to be cognitively overridden (MacLeod & Ruthenford, 1992), but there appears to be evidence for preattentive biases towards stress as a vulnerability factor in non-clinical groups (Pury, 2002; Van den Hout et al., 1995; MacLeod & Hagan, 1992). Accordingly, in the non-clinical sample of women with fertility problems, we expected a positive relationship between preattentive biases towards threat and change in anxiety after an unsuccessful treatment.

## **Method**

### *Subjects*

The sample consisted of a total of 49 women who entered the IVF programme at the University Medical Centre St. Radboud from January 1999 to June 2000 and who did not get pregnant after their first treatment cycle. Three to seven days before the start of treatment, these women completed questionnaires ( $T_1$ ). In the same period, an emotional Stroop task was administered. Four weeks after the pregnancy test, a second questionnaire was administered ( $T_2$ ).

### *Materials*

#### Self-report measures

Neuroticism was assessed with the Dutch version of the Eysenck Personality Questionnaire (Sanderman, Arrindell, Ranchor, Eysenck & Eysenck, 1995). State and trait anxiety were measured using the Spielberger state and trait anxiety questionnaire (STAI, Dutch translation: Van der Ploeg, 2000; Spielberger 1983). As a control factor, depression was measured with the Dutch version of the BDI (Bouman et al., 1985; Beck, 1976). The state anxiety and depression questionnaires were repeated four weeks after the pregnancy test was administered in the first treatment cycle, at  $T_2$ .

### Stroop: equipment and procedure

We used a PC with a Pentium Processor motherboard and a high-resolution Trinitron colour monitor (Sony, multiscan 15 inch). One button was linked to the computer in order to enable the researchers to score incorrect responses. The test was administered in a room devoid of daylight, with a single light source located behind the monitor. Light intensity was constant throughout the sessions. Reaction time was recorded with a microphone placed 5 cm in front of patients' mouths.

We administered a single trial format of the Stroop, consisting of fifteen neutral words, fifteen general threat words (e.g. blood, torture, pain) and six threat words related to infertility, presented in three colours: blue, red and green. We used the same set of neutral and general threat words as Van den Hout et al. (1995). The threat words were related to physical and social threats (e.g. war, torture, lies, despair, accidents, death). The selection of infertility-related threat words was based on a word valence study performed with 30 IVF or ICSI patients and 12 controls. The women in the control group were the same age as the IVF and ICSI women. Narratives on infertility problems were used to select 35 words of possible valence for women with fertility problems. These words were presented on paper with two 5-point Likert scales for each word. On the first scale, women could indicate the positive value of the various words, on the other they could indicate the negative value of the words. The following six words in English (followed by the Dutch translation between brackets) that scored highest on negative valence after subtracting the positive valence were selected for the use in the Stroop experiment: 'infertile' [onvruchtbaar], 'miscarriage' [miskraam], 'childless' [kinderloos], 'bleeding' [bloeding], 'bellyache' [buikpijn], and 'period' [ongesteld].

The general threat words and the neutral words were matched in terms of the same number of syllables and lexical frequency. The specific threat words could not be matched in terms of the number of syllables because there were no specific threat words available with one or four syllables. The mean number of syllables in the general threat and neutral words was 2.1 and in the specific threat words 2.5. Subliminal and supraliminal exposure conditions were employed. First, the words were presented subliminally for 12 msec. After 12 msec, a mask appeared in the same place where the word had appeared. The scale and colours of the mask were the same as those of the word. Seven seconds before presentation of the word with or without mask, a white dot was presented where the word was to appear.

After the subliminal trials (N=108), the supraliminal version was administered, also with a random sequence of words and colours. The supraliminal Stroop task was administered in a consecutive sample of 59 women who had already participated in a subliminal Stroop task. Accordingly, one Stroop session consisted of 108 trials presented subliminally and 108 trials presented supraliminally. Subliminality was checked by a lexical decision task administered after the experimental trials. Performance was chance (differences in amount of false responses to real versus nonsense words:  $t(94)=0.25$  ;  $p=0.80$ ).

To avoid priming effects of words presented supraliminally, the subliminal trials were presented before the supraliminal trials (see also Fox, 1996).

#### General procedure

The Stroop task was administered in hospital at the department of Medical Psychology. Women were asked to participate in a reaction-time experiment as part of a study on the emotional aspects of IVF or ICSI treatment. They sat in front of the computer screen and were instructed to say the colour of the material presented as quickly as possible into the microphone in front of them. Before the start of the first trial, ten practice trials were administered to instruct the patients on how loudly to say the colour of the presentation appearing on the screen. After administration of the Stroop task, the women were asked to complete the questionnaire on neuroticism, trait and state anxiety and depression. Four weeks after the pregnancy test, they received a second questionnaire by post at home. They were asked to complete the questionnaire and return it within two weeks in the enclosed, prepaid envelope.

#### *Statistical analyses*

To investigate interference differences between threat and neutral words, difference scores were calculated by subtracting reaction time on neutral words from reaction time on threat words (in conformity with Van den Hout et al.; 1995). This revealed two measures for subliminal threat interference indices and two for supraliminal threat interference: the subliminal general threat interference index (GTII-sub) is reaction time on neutral words subtracted from reaction time on general threat words in the subliminal presentation mode. The subliminal specific threat interference index (STII-sub) is reaction time on neutral words subtracted from reaction time on fertility-related threat words in the subliminal presentation mode. The same applies to the supraliminal presentation mode (GTII-sup and STII-sup). A

positive value on these threat interference indices means a slower reaction time on threat words, compared with neutral words.

Trials with an incorrect answer were omitted from analysis, just as trials with a reaction time more than three SDs above or below mean reaction time.

Student's t-tests were used to measure differences in reaction time on the different word types and presentation modes (subliminal and supraliminal). ANOVAs were performed in order to control for the effects of differences in word length between the three word types.

Pearson's correlation coefficients were determined in order to examine the concurrent relationship of neuroticism, trait anxiety and Stroop interference factors to state anxiety. These correlational analyses were repeated after controlling for depression at baseline in order to control for the confounding effect of depression (Mogg, Bradley, Williams & Mathews, 1993b).

To investigate the predictive value of the Stroop threat interference indices, sequential regression analyses were carried out, with state anxiety after the unsuccessful treatment as dependent variable. Baseline measures of state anxiety were entered in the first step, neuroticism and trait anxiety in the second step, and subliminal Stroop interference indices in the third step. Standardised Beta coefficients for all variables in the model were calculated to allow comparison of the relative importance of variables entered. Additional regression analyses were carried out in a subsample of women showing an increase in state anxiety between  $T_1$  and  $T_2$  (residual gain score  $\geq 0$ ). These regression analyses were performed in the same way as those in the total sample.

To investigate the interaction between neuroticism and both subliminal Stroop interference factors, interaction terms were determined by multiplying the z-scores of neuroticism by the z-scores of the interference indices.

## Results

The mean age of the women was 33.5 years ( $SD=4.1$ ). At pretreatment ( $T_1$ ), the mean score for trait anxiety (STAI) was 36.8 ( $SD=7.7$ ), for state anxiety (STAI) 36.5 ( $SD=8.9$ ), for depression (BDI) 5.7 ( $SD=4.3$ ), and for neuroticism 4.4 ( $SD=2.9$ ).

There was a significant increase in state anxiety from pretreatment to posttreatment measurements ( $t(48)=-2.09$ ;  $p=0.04$ ). Depression too,

increased significantly ( $t(48)=-2.70$ ;  $p=0.01$ ) after the first unsuccessful treatment cycle.

Table 1 gives the mean reaction times on the three word types in the subliminal and supraliminal condition.

**Table 1.** Reaction time to different word types, subliminal and supraliminal in msec. (N=49)

	Subliminal		Supraliminal	
	Mean	SD	Mean	SD
<b>Reaction time</b>				
to neutral words	628	100	672	114
to general threat words	627	100	669	114
infertility-related threat words	628	101	698	132

T-tests on mean differences did not reveal any significant subliminal differences between either general ( $t(48)=-0.18$ ;  $p=0.86$ ) and infertility-related ( $t(48)=0.10$ ;  $p=0.92$ ) threat words, and neutral words. In addition, no differences in interference were found between supraliminal general threat words and neutral words ( $t(48)=0.66$ ;  $p=0.52$ ). However, there was a significant difference in supraliminal Stroop interference on infertility-related words and neutral words ( $t(48)=-2.13$ ;  $p=0.04$ ).

#### *Concurrent relationship to state anxiety*

To investigate the relationship of neuroticism and preattentive and attentional biases towards threat to state anxiety prior to IVF or ICSI treatment, Pearson's correlation coefficients between these factors were calculated. These correlations are provided in Table 2.

A significant relationship was found between both state anxiety and neuroticism, and trait anxiety. There were no significant relationships found between state anxiety and general subliminal Stroop interference indices and a trend towards a relationship between state anxiety and infertility-related subliminal Stroop interference indices. In addition, correlation analyses between state anxiety and supraliminal interference indices did not reveal any significant relationships.



**Table 2.** Correlations between subliminal and supraliminal General Threat Interference Indices (GTII) and Infertility-related Threat Interference Indices (ITII), neuroticism, trait and state anxiety and depression prior to IVF or ICSI treatment and state anxiety and depression after unsuccessful treatment (N=49)

	Subl GTII	Subl ITII	Supr GTII	Supr ITII	Neuro ticism	Trait Anx.	State Anx.T <sub>1</sub>	Depr. T <sub>1</sub>	State Anx.T <sub>2</sub>
Subl ITII	0.37**								
Supr GTII	0.18	0.18							
Supr ITII	0.02	0.18	0.27*						
Neuroticism	-0.02	-0.08	0.04	0.04					
Trait Anx.	0.00	0.11	-0.18	0.14	0.44**				
State Anx. T <sub>1</sub>	-0.15	0.25	-0.11	-0.14	0.19	0.29*			
Depr. T <sub>1</sub>	0.06	0.02	-0.08	-0.06	0.34**	0.41**	0.35*		
State Anx. T <sub>2</sub>	-0.22	0.27	-0.20	-0.04	0.54**	0.49**	0.45**	0.48**	
Depr. T <sub>2</sub>	0.01	-0.02	0.02	0.06	0.36*	0.39**	0.11	0.65**	0.48**

\*  $p < 0.05$ ; \*\*  $p < 0.01$

To control for a possible suppressive effect of depression at baseline on the Stroop interference indices (Mogg et al., 1993a), partial correlations between trait and state anxiety and TII were calculated, controlling for depression at baseline. These partial correlations did not demonstrate any significant relationships between anxiety and interference factors (coefficients ranged from -0.13 ( $p=0.22$ ) to 0.16 ( $p=0.12$ ). Accordingly, depression at baseline did not significantly confound the threat interference indices.

To explore whether the relationship between preattentive bias towards threat and state anxiety was dependent on levels of trait anxiety, a subsample of women was selected on the basis of their trait anxiety scores. The median split method was used as cut-off criterion. In the subgroup of women scoring above the median, additional correlations were calculated between Stroop interference and state anxiety. Again, these correlations were insignificant (GTII state anxiety:  $r=-0.13$ ;  $p=0.58$ ; ITII state anxiety:  $r=0.19$ ;  $p=0.39$ ).

*Prospective relationships to change in anxiety after the first unsuccessful treatment cycle*

To identify the predictive value of both neuroticism and subliminal Stroop interference prior to treatment, regression analyses were carried out with neuroticism, trait anxiety and subliminal Stroop interference indices as predictors, and changes in state anxiety after the unsuccessful treatment as dependent variable. In the first step, baseline levels of state anxiety were entered, followed by neuroticism and trait anxiety in the second step and both subliminal threat interference indices in the third step. The results of the regression analyses are provided in Table 3.

**Table 3.** Regression analyses predicting change in anxiety after the unsuccessful treatment (N=49); p values between parentheses

	<b>Beta</b>	<b>t</b>	<b>Delta R<sup>2</sup></b>
Pretreatment anxiety	0.32	2.89 (0.01)	0.27 (<0.01)
Neuroticism	0.41	3.63 (<0.01)	0.24 (<0.01)
Trait anxiety	0.20	1.73 (0.10)	
Subliminal interference			0.06 (0.06)
General threat words	-0.19	-1.74 (0.09)	
Fertility-related words	0.26	2.31 (0.03)	

After controlling for baseline levels of state anxiety, the analyses revealed that neuroticism significantly predicted a change in state anxiety (beta=0.41;  $p<0.01$ ), followed by subliminal interference on infertility-related threat words (beta=0.26;  $p=0.03$ ). Trait anxiety and subliminal general threat interference did not explain additional variance. So higher levels of neuroticism, together with more interference on subliminally presented infertility-related threat words, predicted greater increase in state anxiety after the first unsuccessful treatment cycle. However, it has to be noted that, in addition to neuroticism and trait anxiety, the relative contribution of subliminal threat interference to the change in state anxiety tended toward significance ( $p=0.06$ ). To investigate the possible effect of the interaction between neuroticism and both Stroop interference factors, two interaction terms were added into the fourth step of the regression analyses. This did not reveal any significant results.

The same regression analyses were performed using the two supraliminal Stroop interference indices as predictors, in addition to neuroticism, trait and state anxiety. These analyses did not reveal any significant results (Delta  $R^2$  of supraliminal Stroop interference indices =0.01;  $p=0.81$ ).

Theories that propose a relationship between preattentive biases towards threat and the emotional response to a stressor assume that these biases make them more vulnerable to develop higher levels of anxiety when under stress (Mogg & Bradley, 1998; Williams et al., 1996). This means that the occurrence of a stressor is a condition for making this vulnerability obvious. Accordingly, it is possible that the results could be more pronounced in a sample of women who show an increase in anxiety from pretreatment to posttreatment assessments.

**Table 4.** Regression analyses predicting change in anxiety after the unsuccessful treatment failed (subgroup with high change in anxiety;  $N=25$ ),  $p$  values between parentheses

	Beta	t	Delta $R^2$
Pretreatment anxiety	0.49	3.04 (0.01)	0.34 (0.01)
Neuroticism	0.39	2.39 (0.03)	0.10 (0.25)
Trait anxiety	0.13	0.82 (0.43)	
Subliminal interference			0.21 (0.03)
General threat words	0.12	0.68 (0.51)	
Fertility-related words	0.41	2.16 (0.05)	

That is why additional regression analyses were conducted in a subgroup of patients who showed an increase of anxiety between pretreatment and posttreatment assessments ( $N=25$ ). The cut-off score was based on the residual gain scores of regression of pretreatment anxiety on posttreatment anxiety (residual gain score  $\geq 0$ ). Table 4 shows that neuroticism (beta=0.39;  $p=0.03$ ) and interference on subliminally presented fertility-related words (beta=0.41;  $p=0.05$ ) at pretreatment assessments were predictors of higher levels of anxiety after the first treatment, after controlling for pretreatment levels of anxiety. The reduced explained variance of neuroticism in the subsample is due to the reduction of variance in change in anxiety in this sample (correlation between neuroticism and

change in anxiety  $r=0.52$ ). As in the total sample, trait anxiety and subliminal interference on general threat words did not explain additional variance in state anxiety.

Higher levels of neuroticism and subliminal infertility-related Stroop interference at pretreatment predicted greater increase in anxiety after unsuccessful treatment. The prediction was more pronounced in a subgroup of women who showed an increase of anxiety in response to the unsuccessful treatment. Interference on subliminally presented infertility-related threat words was the only Stroop factor that significantly predicted posttreatment anxiety.

## Discussion

The first aim of the study was to explore the concurrent relationship of neuroticism, trait anxiety and preattentive and attentional biases towards threat to state anxiety in a non-clinical sample. As expected, we found support for the existence of a relationship between both neuroticism and trait anxiety to state anxiety. However, we could not identify a relationship between either supraliminal or subliminal interferences with state anxiety. We only identified a trend towards a relationship between state anxiety and infertility-related preattentive Stroop interference indices. The absence of a relationship between supraliminal attentional bias and state anxiety corresponded to results from other studies (Fox, 1996; Mogg et al., 1993<sup>a</sup>; MacLeod & Ruthenford, 1992). A relationship between subliminal Stroop interference and state anxiety, however, was found in some studies (Van den Hout et al., 1995; MacLeod & Hagan, 1992), while not in others (Mogg et al., 1993<sup>a</sup>; MacLeod & Ruthenford, 1992). It is possible that the different results were due to a lack of power of the present and previous studies.

Another explanation for the absence of a relationship between subliminal Stroop interference and state anxiety in the present study could be the possible suppressive effect of depression on interference on threat-related words (Mogg et al., 1993<sup>b</sup>). But correlational analyses controlling for baseline levels of depression did not reveal significant results.

The moderate levels of trait and state anxiety in the sample could be another reason for lack of support for the hypothesis of a positive relationship between state anxiety and subliminal attentional bias towards threat. Additional analyses in a subgroup of women with high levels of trait anxiety did not reveal significant results.

Another explanation for lack of a relationship between preattentive and attentional biases and state anxiety might be the blocked design with respect to the presentation mode we used in our study. This design was employed to prevent temporary activation of the fear structure as a result of presentation of supraliminal words (see also Fox; 1996). The absence of this priming effect may explain the lack of significant relationships between preattentive biases towards threatening information and state anxiety in the present study.

The second aim of the study was to investigate the relationship between neuroticism, trait anxiety and a preattentive bias towards threat with a change in state anxiety after an unsuccessful IVF treatment. As expected, regression analyses revealed an additional explanation of variance in change of anxiety by subliminal Stroop interference, together with neuroticism. Trait anxiety did not, however, explain additional variance.

These results support theories that assume preattentive biases towards threat as vulnerability factors in the development of anxiety (Mogg & Bradley, 1998; Williams et al., 1996). Accordingly, they replicated results of empirical studies that showed a relationship between pre-stressor preattentive biases towards threat and post-stressor assessments of emotional states (Pury, 2002; van den Hout et al., 1995; MacLeod & Hagan, 1992). In the present study, the relationship between preattentive biases and changes in anxiety was first demonstrated. In addition, the present study controlled for levels of neuroticism and trait anxiety. Even after controlling for this negative affectivity on strategic level, as indicated by self-report measures of neuroticism and trait anxiety, preattentive biases towards threat explained additional variance. This result brought up the question of the relationship between preattentive biases towards threat and neuroticism or trait anxiety. A positive relationship between these vulnerability factors would be expected, but the results of the present study did not support this (see Table 2). It seems as if preattentive biases towards threat and indications of negative affectivity as indicated in self-report measures from personality questionnaires are the results of different processes. Further research is needed to clarify the relationship between these different types of vulnerability factors in non-clinical samples.

A significant issue that we have not so far been discussed is the predictive power of infertility-related threat words, compared with that of interference on general threat words. More subliminal bias towards infertility-related threat words predicted higher levels of anxiety as a result of the

unsuccessful treatment, whereas a subliminal bias towards general threat words did not predict changes in anxiety. The subliminal bias towards infertility-related threat words might be an indication that infertility-related stimuli more easily triggered the fear structure than general threat stimuli. It seems as though the attention paid to stressor-related stimuli at the beginning of processing threatening information gave a better indication of vulnerability to a higher anxiety response to the unsuccessful treatment than attention paid to general threatening stimuli. Comparison with other studies cannot provide definite answers, because the studies that prospectively investigated the subliminal Stroop factors did not differentiate between general and stressor-related stimuli. While subliminal Stroop interference on infertility-related words predicts anxiety response to an unsuccessful IVF or ICSI treatment, the subliminal Stroop interference on general threat words could predict emotional response to a more life-threatening stressor. Further research might clarify this.

How do the results of the present study contribute to vulnerability models for developing anxiety? It was clear from the outset that personality factors, such as measured by self-report inventories, have predictive value for the development of anxiety. In previous studies, preattentive and attentional biases towards threatening information were proved to be associated with clinical anxiety. Little was known, however, about the value of these biases in a vulnerability model for explaining the development of anxiety in a general, non-clinical population. Neither was it clear to what extent both kinds of factors (personality factors and preattentive and attentional biases) are interrelated in the development of anxiety. This study shows that both neuroticism and preattentive biases towards threatening information are vulnerability factors for the development of higher levels of anxiety as the result of a severe stressor in a non-clinical sample. Accordingly, the results underline the importance of preattentive biases towards threat as an additional vulnerability factor in the development of anxiety.



## Chapter 5

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### Predicting emotional response to unsuccessful fertility treatment, a prospective study

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## **PREDICTING EMOTIONAL RESPONSE TO UNSUCCESSFUL FERTILITY TREATMENT, A PROSPECTIVE STUDY**

### **Abstract**

The predictive value of a comprehensive model with personality characteristics, stressor related cognitions, coping and social support was tested in a sample of 187 non-pregnant women. The emotional response to the unsuccessful treatment was predicted out of vulnerability factors assessed before the start of the treatment. The results indicated the importance of neuroticism as a vulnerability factor in emotional response to a severe stressor. They also underlined the importance of helplessness and marital dissatisfaction as additional risk factors, and acceptance and perceived social support as additional protective factors, in the development of anxiety and depression after an unsuccessful fertility treatment. From clinical point of view, these results suggest that fertility-related cognitions and social support should receive attention when counselling women who undergo IVF or ICSI treatment.

### **Introduction**

In the Netherlands, one out of 55 children is born out of an in vitro fertilization (IVF) or intracytoplasmic sperminjection (ICSI) pregnancy, and the incidence of IVF or ICSI treatment continues to increase (Kremer et al., 2002). Both IVF and ICSI treatment involve many stressful aspects. There is the physical stress of the treatment itself which requires repeated self injections with hormonal medication for several weeks, retrieval of mature oocytes from the ovaria and in case of fertilization, transfer of the embryos into the womb. Dealing with the threat of the treatment itself can cause anxiety (Boivin & Takefman, 1995). In addition, there is the emotional stress of a possible failure. In most cases, IVF or ICSI treatment is the last chance for pregnancy. One treatment consists of different cycles. After one treatment cycle only twenty to twenty-five percent of the women involved become pregnant, while after three cycles still about fifty percent of the women are faced with failure. After three unsuccessful cycles, the chance of pregnancy is slight (Stolwijk et al., 1996) and women have to adjust to the loss of their hope of ever becoming pregnant. This loss can evoke feelings of depression (Verhaak et al., 2001; Beaurepaire et al., 1994; Visser et al., 1994; Berg & Wilson, 1991; Baram et al., 1988).

Before couples start an IVF or ICSI treatment, most of them have already dealt with fertility problems for several years (Mazure & Greenfeld, 1989), making the stress of the threatening infertility a relatively chronic one. Since little can be done by patients themselves to enhance the possibility of a pregnancy, the stressor of the treatment and the threatening infertility is considered as highly uncontrollable (Miller-Campbell et al., 1991). The longstanding nature of this stress combined with the lack of control makes the stressor of infertility comparable to other uncontrollable long term stressors such as a chronic disease (Domar et al., 1993).

Studies on the emotional response to an unsuccessful IVF or ICSI treatment have indicated that most of the couples adjust well to the failure but a subgroup develops severe emotional problems (Reading et al., 1989). From a clinical point of view, it is important to know in advance which women are vulnerable to develop these problems, so that additional counselling can be offered at an early stage.

Differences in the emotional response to a severe stressor are assumed to be determined by several factors described in vulnerability or diathesis stress models (Costa et al., 1996; Holahan et al., 1996; Ormel & Wohlfart, 1991) such as personality characteristics (Clark et al., 1994; Edelmann, 1992; Eysenck, 1981), stressor related cognitions (Alloy et al., 1999; Leventhal et al., 1984; Beck et al., 1979; Abramson et al. 1978), coping (Holahan & Moos, 1985; Lazarus & Folkman, 1984), and social support (Cohen & Wills, 1985).

With respect to personality characteristics, there is considerable evidence that higher levels of neuroticism predict higher levels of negative emotional response, whereas extraversion and optimism seem to be predictive for a more positive emotional response to general stressors (Clark et al., 1994; Carver et al., 1993; Hotard et al., 1989; Watson & Clark, 1984; Costa & McCrae, 1980) and, more specifically to long term, uncontrollable stressors (Evers et al., 2002; Carver et al., 1993). In terms of IVF and ICSI treatments, the relationship between personality factors and emotional response to treatment has been investigated only slightly. Only optimism has been taken into account and has been shown to be predictive for less distress after a lack of success in the first cycle (Litt et al., 1992).

In addition to personality characteristics, stressor related cognitions, as indications of the evaluation of the stressor, are also supposed to play an important role in the vulnerability to psychopathology in general life (Alloy et al., 1999; Beck et al., 1979;) and when facing severe stressors (Davis &

Nolen-Hoeksema, 2001; Evers et al., 2001; Holahan et al., 1996; Leventhal et al., 1984). Cognitions of helplessness and cognitions of acceptance have been shown to predict the emotional response to the stressor, specifically in responses to uncontrollable stressors (Evers et al., 2001; Smith et al., 1994; Carver et al., 1993;). Accordingly, helplessness resulting from loss of control, was associated with more distress (Miller- Campbell et al., 1991). In a study with a prospective design, acceptance as a result of a re-evaluation of the stressor, was predictive of a more positive course of the emotional response after an unsuccessful IVF or ICSI treatment cycle (Terry & Hynes, 1998).

As a way to deal with the stressor, coping is assumed to play a major role in the relationship between a stressor and the emotional response (Holahan et al., 1996; Aldwin, 1994; Lazarus & Folkman, 1984). An active coping style is supposed to be related to a more positive emotional response to a stressor in general, and, more specifically, to health problems (for a review see: Holahan et al., 1996; Aldwin, 1994;). Empirical evidence for the effectiveness of an active coping style however, is equivocal, possibly due to high context specificity of active coping depending on the characteristics of the stressor (Penley et al., 2002; Suls & Fletcher, 1985). More consistent evidence is found for a prospective relationship between higher levels of avoidant coping and a more negative emotional response to stressors (Stanton et al., 2000; Pakenham, 1999; Terry & Hynes, 1998; Carver et al., 1993). It has also been shown among women undergoing fertility treatment, that an avoidant coping style before treatment is predictive of a more negative emotional response after the treatment (Litt et al., 1992).

Social support is supposed to be a protective factor (Holahan et al., 1996), positively related to adjustment to a stressor (see e.g. Valentiner et al., 1994; Cohen & Wills, 1985;). In the context of women entering IVF or ICSI treatment, the marital and sexual relationship is seen as the most important source of support (Laffont & Edelmann, 1994<sup>b</sup>). A high-quality marital and sexual relationship could provide protection against higher negative emotional response to the unsuccessful treatment. To date however, there is a lack of studies that prospectively investigated that role of the quality of the marital and sexual relationship as a predictor in the adjustment to an unsuccessful IVF or ICSI treatment. In addition to the marital and sexual relationship, more general aspects of social support, especially perceived social support and the size of the social network have been shown to

positively affect the emotional response to a stressor in a general population (Holahan et al., 1996), as well as to a specific uncontrollable stressor (e.g. Evers et al., 1997).

So far, empirical evidence supports a link between several vulnerability factors and the emotional response to an unsuccessful IVF or ICSI treatment cycle. However, empirical evidence is mostly limited to cross sectional studies. The few longitudinal studies available, did not predict change in emotional response from pretreatment to posttreatment assessments (Terry and Hynes, 1998; Litt et al., 1992). This means that information about factors that could predict emotional response to an unsuccessful treatment cycle and the relative contribution of these factors to emotional response cannot be drawn from existing research.

The aim of the present study was to examine the role of a comprehensive set of vulnerability factors in the prediction of the emotional response to an unsuccessful IVF or ICSI treatment cycle. Information about factors that could predict the emotional response provide the opportunity to gain insight in the focus of possibly timely intervention for women at risk of developing emotional problems as a result of an unsuccessful treatment cycle. Specifically, the focus of interest was the contribution of stressor related cognitions, coping and social support, above the impact of personality characteristics. Accordingly, in the present study, the central question was: What is the additional predictive value of infertility-related cognitions, coping and social support after controlling for baseline levels of anxiety and depression and personality characteristics for emotional response to an unsuccessful IVF or ICSI treatment cycle. We expected higher levels of neuroticism, lower levels of extraversion and optimism, higher levels of helplessness and lower levels of acceptance, less active problem-focussed coping and more passive, avoidant coping, greater dissatisfaction with the marital and sexual relationship and less perceived social support and social integration to be predictive for an increase in anxiety and depression as the result of an unsuccessful IVF or ICSI treatment cycle.

## **Method**

### *Participants*

Participants were recruited from a university hospital in the Netherlands. Three hundred and eighty-six women treated by the IVF department in 1999 and 2000 for their first IVF or ICSI treatment agreed to participate in

the study. After the first treatment cycle, 101 women (25%) conceived. Of the 285 non-pregnant women after one treatment cycle, 187 (66%) completed both the pre and posttreatment assessments.

Mean age of the women was 34.3 years (range=21-43). The educational level was low for 32% of the women, moderate for 38% and high for 30% of the women. Mean duration of the fertility problems was 3.3 years (range=0-13). Before the start of the treatment, 17 percent of the women had one or more children. The causes of the fertility problems were female causes (22%), male causes (35%), both female and male causes (10%) and idiopathic causes (33%).

T-tests did not reveal any significant differences in anxiety, depression, age and educational level, among the women who completed both the pre and posttreatment questionnaires and the women who dropped out of the study after the first treatment cycle.

#### *Procedure*

Women were asked to participate in the study when at the hospital for an intake interview with their physician prior to their first IVF/ICSI treatment cycle. After obtaining written informed consent, the questionnaires were sent to their homes. Participants were asked to complete the questionnaires five to ten days before the start of medication ( $T_1$ ) and return them in a prepaid envelop to the hospital. Four weeks after the pregnancy test subsequent to the first treatment cycle, a second set of questionnaires was sent by post ( $T_2$ ). The average time between  $T_1$  and  $T_2$  was about three months (range 11 to 15 weeks).

Background characteristics, personality characteristics, infertility related cognitions, coping, social support, anxiety and depression were assessed at  $T_1$ . Measurements of anxiety and depression were repeated at  $T_2$ .

The study was approved by the ethical committee of research with humans of the University Medical Center.

#### *Measures*

Educational level and medical characteristics related to the success rate of the treatment as defined by Templeton et al. (1996) (age, duration and causes of fertility problems and number of children) were assessed with a general questionnaire.

Three personality factors were measured: neuroticism, extraversion and optimism. Neuroticism and extraversion were measured with two subscales

of the Dutch version of the Eysenck Personality Questionnaire (Sanderman et al., 1995). The possible range of both scales was 0 to 12. Cronbach's alphas in the present study were 0.81 for neuroticism and 0.79 for extraversion. Optimism was assessed with the optimism scale of the Life Orientation Test (LOT: 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 0.81.

Infertility related cognitions of helplessness and acceptance were measured with the 'Illness Cognitions Questionnaire' (Evers et al., 2001) that was adjusted to the situation of women facing fertility problems. The six helplessness and six acceptance (possible range of both scales=6-24) items are presented in Appendix 1. In the present study, Cronbach's alpha was .86 for the helplessness scale and 0.89 for the acceptance scale.

Coping was assessed with the Utrecht Coping List (UCL; Schreurs et al., 1993), partly adopted from Westbrook (1979). This inventory measures coping strategies when dealing with everyday problems on a 4-point Likert scale. Two scales of the questionnaire were used: active problem focusing (7 items; range=7-28) and avoidance (9 items; range=9-36). The active problem solving scale measures cognitive and behavioral efforts to apply goal oriented problem solving strategies (to see problems as a challenge, take direct action, to think of different solutions). The avoidance scale describes ways to avoid and to steer clear of the problem (to avoid difficult situations, to tolerate the situation, to wait, trying to stay calm, to let things slide assessing efforts to avoid confrontation with the stressor). In the present study, Cronbach's alpha was 0.76 for the active problem solving scale and 0.77 for the avoidance scale.

As indicators of social support, satisfaction with the marital and sexual relationship as well as general aspects of social support, were assessed. Marital and sexual satisfaction were 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 more dissatisfaction. Cronbach's alpha in the present study was 0.85 for general marital satisfaction and 0.70 for sexual satisfaction.

General aspects of social support were measured with a Dutch self-report questionnaire 'Inventory for Social Support' (Van Dam-Baggen & Kraaijmaat, 1992), which measures the size of the social network (by asking for the number of friends and acquaintances) and perceived social support

(possible range=5-20). In the present study, Cronbach's alpha was 0.87 for perceived social support.

State anxiety and depression were assessed with two standardised questionnaires, validated to 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; possible range=20 - 80). Cronbach's alpha was 0.90 for state anxiety. Depression was measured with the Beck Depression Index (BDI; Beck et al., 1976; possible range 0-80). Cronbach's alpha was 0.84.

### *Statistical analyses*

Paired t-tests were performed to examine changes in emotional status between pre and posttreatment assessments. Pearson's correlation coefficients (in the event of nominal variables, Kendall's rank correlation coefficient was used) were calculated between the vulnerability factors and change scores for anxiety and depression to explore the relationship between background characteristics and vulnerability factors assessed pretreatment, and changes in emotional status between pretreatment ( $T_1$ ) and posttreatment ( $T_2$ ) assessments. Residual gain scores were used as change scores (Kerlinger, 1975). Factors that correlated significantly with these change scores were entered in several regression analyses. These analyses were performed sequentially for anxiety or depression at  $T_2$  as dependent variables, levels of anxiety and depression at  $T_1$  were entered as first predictors. Next, personality characteristics were entered in the second step, followed by, separately, those additional predictors that correlated significantly with change scores in anxiety or depression in the third step. Then, the full models were tested to predict anxiety and depression at  $T_2$  with baseline levels of anxiety or depression in the first step, personality characteristics in the second step, in the third step fertility related cognitions and coping, and social support in the fourth step.

Moderator effects were explored by calculating centered interaction terms between the predictor and the moderator and entering them in the regression analyses, after controlling for their main effects. Mediating effects were explored with the procedure described by Baron and Kenny (1986).



## Results

### *Level and change in anxiety and depression*

Levels of anxiety and depression in the women undergoing their first IVF or ICSI treatment did not differ significantly from age and sex related norm groups (Verhaak et al., 2001). Mean levels of state anxiety were 37.4 (SD=10.8) at T<sub>1</sub> and 39.2 (SD=11.2) at T<sub>2</sub>. Mean depression scores were 6.5 (SD=5.9) at T<sub>1</sub> and 7.5 (SD=6.4) at T<sub>2</sub>. Paired t-tests revealed a significant increase in both anxiety and depression after the first unsuccessful treatment cycle (anxiety:  $t(186)=-3.24$ ;  $p<0.01$ ; depression:  $t(186)=-3.31$ ;  $p<0.01$ ).

Means and standard deviations for personality characteristics, infertility related cognitions, coping and social support at first assessments are presented in Table 1.

**Table 1.** Means and standard deviations of demographic and psychological variables before treatment in 187 non-pregnant women

	T <sub>1</sub>	
	Mean	SD
Personality characteristics		
Neuroticism	4.7	3.0
Extraversion	7.6	1.9
Optimism	13.5	2.8
Infertility related cognitions		
Helplessness	11.5	5.3
Acceptance	13.6	4.9
Coping		
Active problem focusing	18.6	3.3
Avoidance	16.4	3.1
Social support		
Marital dissatisfaction	19.9	7.4
Sexual dissatisfaction	6.1	6.1
Perceived social support	16.9	2.9
Size of the social network	8.4	1.9

*Background characteristics and change in anxiety and depression*

At first, correlational analyses were performed to investigate relationships between educational level, medical parameters and changes in anxiety and depression between pre en posttreatment measurements. These analyses revealed no significant correlations between changes in anxiety and depression (residual gain scores) and educational levels, age and duration of the fertility problems. Nonparametric correlational analyses did not reveal any significant correlation between change in anxiety and depression and different causes of the fertility problems, nor between women with and without children.

*Prediction of emotional response to the unsuccessful treatment*

The correlations between predictors, measured at baseline, and change in anxiety and depression between T<sub>1</sub> and T<sub>2</sub> are provided in Table 2.

**Table 2.** Correlations between predictors at T<sub>1</sub> and change in anxiety and depression after the unsuccessful treatment

	Change in anxiety	Change in depression
Personality characteristics:		
Neuroticism	0.25**	0.22**
Extraversion	-0.05	-0.09
Optimism	-0.09	-0.05
Infertility-related cognitions		
Helplessness	0.22**	0.28**
Acceptance	-0.21**	-0.26**
Coping		
Active problem solving	0.01	0.01
Avoidance	-0.00	-0.04
Social support		
Marital dissatisfaction	0.22*	0.11
Sexual dissatisfaction	-0.03	-0.00
Perceived social support	-0.11	-0.29**
Size of the social network	0.00	-0.01

\*\* p=<0.01; \* p=<0.05

**Table 3a.** Different models in predicting anxiety, beta coefficients

	model 1		model 2		model 3		full model	
	Beta	Delta R <sup>2</sup>	Beta	Delta R <sup>2</sup>	Beta	Delta R <sup>2</sup>	Beta	Delta R <sup>2</sup>
1. Baseline	0.39**	0.34**	0.38**	0.34**	0.41**	0.34**	0.36**	0.34**
2. Neuroticism	0.25**	0.05**	0.26**	0.05**	0.26**	0.05**	0.22*	0.05**
3. Inf. related cognitions		0.02*		0.02*				0.02*
Helplessness	0.14*						0.07	
Acceptance			-0.14*				-0.12	
4. Marital dissatisfaction					0.13*	0.02*	0.14*	0.02*
Total R <sup>2</sup>		0.41**		0.41**		0.41**		0.43**

\*\* p=<0.01; \* p=<0.05

The increase of anxiety after the first unsuccessful treatment cycle was significantly and positively related to neuroticism, helplessness, and marital dissatisfaction, and significantly and negatively related to acceptance. The increase of depression after the first unsuccessful treatment cycle was significantly and positively related to neuroticism and helplessness, and significantly and positively related to acceptance and perceived social support. No significant correlations were found with the other personality factors (extraversion and optimism), coping, sexual dissatisfaction and size of the social network.

Accordingly, neuroticism, helplessness, acceptance and marital dissatisfaction were involved in the regression analyses to predict change in anxiety. Neuroticism, helplessness, acceptance and perceived social support were taken into account in the prediction of the change in depression.

The first step was to separately identify the relative contribution of fertility-related cognitions and social support factors towards predicting emotional response to an unsuccessful IVF or ICSI treatment.

As is shown in Table 3a and 3b, results indicated that higher levels of neuroticism significantly predicted higher levels of anxiety and depression at T<sub>2</sub> after controlling for pretreatment levels of anxiety and depression. In addition: when entering infertility related cognitions of helplessness (model 1), acceptance (model 2), or marital dissatisfaction (model 3), separately, in

**Table 3b.** Different models in the prediction of depression, beta coefficients

	model 1		model 2		model 3		full model	
	Beta	Delta R <sup>2</sup>	Beta	Delta R <sup>2</sup>	Beta	Delta R <sup>2</sup>	Beta	Delta R <sup>2</sup>
1. Baseline	0.39**	0.36**	0.42**	0.36**	0.39**	0.36**	0.34**	0.36**
2. Neuroticism	0.22**	0.05**	0.22*	0.05**	0.25**	0.05**	0.19*	0.05**
3. Inf. related cognitions		0.04**		0.03*				0.05**
Helplessness	0.22**						0.16	
Acceptance			-0.20*				-0.11	
4. Perceived social support					-0.20**	0.04**	-0.19**	0.03*
Total R <sup>2</sup>		0.45**		0.44**		0.45**		0.49**

\*\* p=<0.01; \* p=<0.05

the third step, all factors contributed significantly additional variance to the prediction of anxiety. Helplessness, acceptance and perceived social support, also separately, added significant variance in the prediction of depression.

The results of the regression analyses of the full model are presented in the last columns of both Tables 3a and 3b. Infertility related cognitions and marital dissatisfaction added significant variance in predicting change in anxiety after controlling for neuroticism. In predicting depression after unsuccessful treatment, infertility related cognitions and perceived social support added significant explanation of variance after controlling for neuroticism.

Moderator effects were explored by entering centred interaction terms between all vulnerability factors in the regression analyses, after controlling for their main effects. Results indicated that none of the interaction terms predicted anxiety or depression after the unsuccessful treatment.

Mediating effects were explored by changing the sequence in the regression analyses. Again, these analyses revealed no differences in results.

To sum up, the results indicated that neuroticism, infertility related cognitions and indicators of social support predicted the change in anxiety and depression after the first unsuccessful treatment cycle.

**Discussion**

A vulnerability model was tested in this study, to predict the emotional response to the stressor of an unsuccessful IVF or ICSI treatment cycle on the basis of vulnerability factors measured before the start of the treatment. Results indicate that infertility related cognitions and social support could predict additional change in anxiety and depression after the unsuccessful IVF or ICSI treatment, after controlling for both pretreatment anxiety, depression and neuroticism.

The predictive value of neuroticism for the emotional response to a severe stressor in several populations is well recognized (Carver et al., 2000; Clark et al., 1994; Hotard et al., 1989). In the few prospective studies on the emotional response to an unsuccessful IVF or ICSI treatment cycle, neuroticism has not been taken into account as a predictor. A study into the related topic of pregnancy loss revealed a significant relation between higher levels of neuroticism and higher grief levels in women after a pregnancy loss, which is in line with the results of the present study (Janssen et al., 1995).

The importance of fertility related cognitions as a predictor for emotional response is in line with recent theories on the influence of cognitive processes in the etiology and maintenance of psychopathology (Leventhal et al., 1984; Beck, 1979). In studies regarding fertility treatment, the importance of fertility related cognitions is frequently recognized (Miller - Campbell et al., 1991; Reading et al., 1989; Abbey & Holmann, 1995; Litt et al., 1992; Newman & Zouves, 1991) but the empirical elaboration has been limited to instruments with questionable reliability, or to cross sectional designs. In the present study, an inventory for assessing both cognitions related to the perceived loss of control (helplessness) and those related to the acceptance of fertility problems revealed consistent results and underlined the importance of these concepts in the adjustment to an unsuccessful treatment cycle. With respect to acceptance, the results of the present study extended the results obtained by Terry and Hynes (1998). They found that problem appraisal coping, a scale quite similar to our acceptance scale, immediately after unsuccessful treatment was an important predictor of the course of emotional response six weeks later. The present study showed that also pretreatment acceptance of possible failure -prior to any failure- predicted posttreatment anxiety and depression. As reported in other studies, the predictive value of avoidant coping was not supported by the IVF or ICSI sample in the present study. Cross-

sectional studies into the relationship between coping and the emotional response to an unsuccessful treatment observed consistent negative effect of avoidant coping prior to treatment to more distress after the unsuccessful treatment cycle (Hynes et al., 1992; Stanton et al., 1992; Cook et al., 1989). More avoidant coping after the unsuccessful treatment was also shown to be related to a more negative course of the emotional response some time later (Terry & Hynes, 1998). Differences between outcomes of these studies and the present one may be due to coping assessment methods. The studies mentioned used coping inventories that assessed escapism or denial, such as daydreaming, unrealistic thinking and acting as if nothing had happened. In this coping strategy, there is no confrontation with the stressor, indicated by behaviour as if nothing has happened. The coping inventory of the present study however, assessed more alleviating aspects of avoidance: trying to avoid people, to wait or to stay calm. This strategy involves at first a confrontation with the stressor, after which further exposure was minimised. In the case of an unsuccessful IVF or ICSI treatment, little can be done to actively change the situation which may be the reason that these types of avoidance were proved not to be significantly maladaptive.

There is a lack of research into the importance of social support, and more specifically, the marital relationship and perceived social support when adjusting to an unsuccessful IVF or ICSI treatment. As far as we know, this is the first study that investigated the role of the marital relationship as a predictor for the emotional response to an unsuccessful IVF or ICSI treatment cycle. In conformation with the hypothesis, social support explained another additional part of the variance in the emotional response to the stressor.

Certain limitations of the present study should be considered. One was the dropout rate between the first and the second measurement points. However, dropout was not selective with respect to psychological and medical factors, and the dropout rate did not differ much from other longitudinal studies (Osowiecki & Compas, 1999; Pakenham, 1999; Epping-Jordan et al., 1999; Terry & Hynes, 1998).

Another limitation of the study is its focus on emotional response to a single unsuccessful treatment cycle. After an unsuccessful cycle, most women will start another treatment cycles within three to six months. Four weeks after the pregnancy test, at the time of the second assessments, a second treatment cycle has not yet started, but it is possible that women at that

moment are already partly looking forward to new chances for pregnancy, which might alleviate the distress of the first failure.

This means that further research into predicting emotional response to consecutive unsuccessful treatment cycles is warranted, without denying the importance of information about the emotional response to a first unsuccessful cycle. It provides an opportunity to gain knowledge about predictors of a short term emotional response to a stressor. Since most women start another cycle after an unsuccessful treatment cycle, with even more chance of failure, emotional response to the first stressor may partly contribute to the response to consecutive stressors.

As far as we know, the present study is the first study that tested a comprehensive model that includes personality factors, cognitions, coping and social support in a normal population, such as women entering IVF or ICSI treatment. What do the results of the present study contribute to general knowledge about stress vulnerability factors in a medical setting? As expected, this study revealed that neuroticism is the most important predictor of the emotional response to a severe stressor such as an unsuccessful IVF or ICSI treatment cycle. The results supported the theories on neuroticism as a general dispositional characteristic of negative affectivity that highly determines the risk of developing more than average emotional problems due to a severe stressor. However, the present study also indicated the additional importance of stressor related cognitions and social support as protective or risk factors in this vulnerability.

The clinical implication of the findings is that infertility related cognitions and social support play an important role in the adjustment to unsuccessful treatment. Even before the start of the treatment, reduced feelings of helplessness, stimulation of acceptance, as well as enhancing social support may positively affect the emotional response to an unsuccessful treatment. The results also underline that clinicians should take multiple factors into account when screening for patients at risk. Pretreatment anxiety and depression levels, neuroticism, fertility-related cognitions of helplessness and acceptance, the marital relationship and the perception of social support are all vulnerability factors when adjusting to an unsuccessful treatment cycle. Interventions focussed on reevaluation of the infertility, working on the marital relationship and on enhancing other aspects of social support might benefit patients at risk. This could result in possible long term positive consequences on the emotional adjustment to one or more unsuccessful treatment cycles.

## Appendix 1

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### Helplessness

1. My infertility frequently makes me feel helpless
2. My infertility limits me in everything that is important to me
3. My infertility controls my life
4. Because of my infertility, I miss the things I like to do most
5. My infertility prevents me from doing what I would really like to do
6. My infertility makes me feel useless at times

### Acceptance

1. I have learned to accept my infertility
  2. I have learned to live with my infertility
  3. I can accept my infertility well
  4. I can cope effectively with my infertility
  5. I think I can handle the problems related to my infertility even if they will not be solved
  6. I can handle the problems related to my infertility
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## **Part 3**

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Long term course of  
anxiety and depression, of satisfaction with  
the marital and sexual relationship,  
and factors that contribute to that course



## Chapter 6

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

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## **A LONGITUDINAL, PROSPECTIVE STUDY ON EMOTIONAL ADJUSTMENT BEFORE, DURING AND AFTER CONSECUTIVE FERTILITY TREATMENT CYCLES**

### **Abstract**

In a longitudinal study involving 148 women and 71 of their partners undergoing IVF or ICSI treatment, we investigated the course of anxiety and depression from pretreatment to six months after their last cycle and we investigated which factors contributed to that course. Self-report questionnaires on anxiety, depression, personality characteristics, cognitions of fertility problems, coping and social support were performed before the start of the first treatment cycle ( $T_1$ ). Assessments of anxiety and depression were repeated immediately after the final cycle ( $T_2$ ) and again six months later ( $T_3$ ). Results revealed an increase in both anxiety and depression in women after unsuccessful treatment between  $T_1$  and  $T_2$ . There was no recovery between  $T_2$  and  $T_3$ . At  $T_3$ , more than 20% of the women showed subclinical forms of anxiety and/or depression. The course of anxiety and depression in women after successful treatment decreased between  $T_1$  and  $T_2$  and stabilized between  $T_2$  and  $T_3$ . Pretreatment levels of anxiety, neuroticism, helplessness and acceptance regarding fertility problems, satisfaction with the marital relationship and social support determined the course of anxiety and depression. Accordingly, a considerable number of women showed subclinical forms of anxiety and depression six months after the last treatment cycle. Timely interventions that focus on cognitions of fertility problems, marital relationship and social support may prevent women from developing these serious emotional problems.

### **Introduction**

In fertility problems both medical and emotional aspects can be distinguished. While the physical impact of the medical treatment is considerable (Evers & Te Velde, 1999), couples considered emotional aspects more stressful (Hammer-Burns & Covington, 2000). For most couples, unsuccessful IVF or 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? In spite of 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 to be 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 of starting a family with one or more children (Dunkel-Schetter & 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 unsuccessful treatment have compared groups of patients in different phases of fertility treatment. These studies revealed high levels of distress in the group of patients who went through more unsuccessful treatment cycles (Boivin et al., 1995; Beaurepaire et al., 1994; Berg & Wilson, 1991). 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 support these findings.

Few prospective studies have been carried out to predict emotional response to fertility treatment (Terry & Hynes, 1998; Litt et al., 1992). These few 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. Apart from 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. Costa et al., 1996; Holahan et al., 1995; Ormel & Wohlfart, 1991;). Neuroticism, cognitions of helplessness when faced with a stressor, avoidant coping and

dissatisfaction with the marital and sexual relationship are identified as risk factors, whereas 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 & Wills, 1985).

In previous studies (Verhaak et al., 2001; Verhaak et al., 2002), we investigated short term emotional response to the first IVF or ICSI treatment cycle. In addition, we investigated a comprehensive model that incorporates several important risk and protective factors in order to predict the short term emotional response to an 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 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.

## **Materials and methods**

### *Participants*

Participants were recruited at a university hospital in a medium-sized city in the Netherlands. Complete data sets for three measurement points were received from a consecutive 148 women and 71 of their partners.

### *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 ( $T_1$ ), and four weeks after the pregnancy test subsequent to the following treatment cycles. For



the present study, data was used from pretreatment assessments ( $T_1$ ) and assessments made just after the final cycle ( $T_2$ ). In addition, follow-up assessments took place six months after this final treatment cycle ( $T_3$ ). To obtain information about how they 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. Psychological and clinical parameters were assessed at  $T_1$ , before the start of the first treatment cycle. Anxiety and depression assessments were repeated at  $T_2$  and  $T_3$ . The average time between  $T_1$  and  $T_3$  was 16 months (range=8-36).

### *Procedure*

Women were asked to participate in the study when they were at the hospital for an intake interview with their physician prior to their first IVF or ICSI treatment cycle. A long protocol with Decapeptyl® and Puregon® 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. Four weeks after each pregnancy test, a subsequent questionnaire was sent by post and a final questionnaire followed six months after the last treatment cycle. The procedure used in subsequent measurement points was the same as used during the first. The study was approved of 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; possible range=20-80). Cronbach's alpha was 0.90 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; possible range=0-28). Cronbach's alpha was 0.84. 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). The possible range of the scale was 0 to 12. Cronbach's alpha in the present study was 0.81. Optimism was assessed with the optimism scale of the 'Life Orientation Test' (LOT: 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 0.81.

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 who faced 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: 'My infertility limits me in everything that is important to me.' An example of the acceptance scale is: 'I can handle the problems related to my infertility.' In the present study, Cronbach's alpha was 0.86 for the helplessness scale and 0.89 for the acceptance scale.

Coping was assessed with the 'Cope' (Carver et al., 1989). 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=0.76), problem appraisal ('behavioural disengagement' and 'positive reinterpretation'; Cronbach's alpha=0.58), emotional approach ('seeking instrumental support,' 'seeking emotional support,' and 'venting emotions'; Cronbach's alpha=0.86), and cognitive avoidance or escapism (Cope factor 'denial'; Cronbach's alpha=0.75). 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 were 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 0.85 for general marital satisfaction and 0.70 for sexual satisfaction.

General aspects of social support were measured with a Dutch self-report questionnaire 'Inventory for Social Support' (van Dam-Baggen & Kraaimaat, 1992), which measures the size of the social network (in terms of the number of friends and acquaintances) and perceived social support (possible range=5-20). In the present study, Cronbach's alpha was 0.87 for perceived social support.

### *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. MANOVAs for repeated measures were performed separately for women 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.

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 pretreatment ( $T_1$ ) and posttreatment ( $T_3$ ) assessments. Residual gain scores were used as change scores (Kerlinger, 1975). These analyses were sequentially performed for anxiety and depression at  $T_3$ , as dependent variables. Levels of anxiety and depression at  $T_1$  were entered as first predictors. Next, personality characteristics were entered in the second step, followed separately by the additional predictors that significantly correlated with change scores in anxiety or depression in the third step.

## **Results**

T-tests did not reveal any pretreatment differences in anxiety ( $t(147) = -0.21$ ;

$p=0.83$ ), depression ( $t(147)=0.48$ ;  $p=0.63$ ), marital dissatisfaction ( $t(147)=0.50$ ;  $p=0.62$ ) or sexual dissatisfaction ( $t(147)=0.74$ ;  $p=0.46$ ) between women whose partners did or did not participate in the study. However, six months after the last treatment cycle, women whose partners did not participate showed higher levels of depression ( $t(147)=3.17$ ;  $p<0.01$ ) and a trend of higher levels of anxiety ( $t(147)=1.79$ ;  $p=0.08$ ) than women whose partners did participate in the study.

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.

**Table 1.** 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  $T_1$  (pretreatment),  $T_2$  (after the final treatment cycle) and  $T_3$  (six months after the final treatment cycle). Standard deviations are between parentheses

	pregnant women	non-pregnant women	men of pregnant women	men of non-pregnant women
state anxiety $T_1$	36.7 (10.1)	37.3 (11.7)	32.8 (6.8)	33.5 (11.7)
state anxiety $T_2$	33.5 (8.7)	40.2 (11.8)	32.3 (6.9)	34.9 (10.2)
state anxiety $T_3$	34.2 (8.5)	39.0 (13.6)	32.3 (8.6)	32.4 (8.0)
depression $T_1$	1.5 (1.8)	1.5 (2.3)	0.7 (0.9)	1.0 (1.3)
depression $T_2$	0.8 (1.3)	2.3 (2.7)	0.6 (0.9)	1.5 (2.2)
depression $T_3$	0.5 (0.9)	2.3 (2.9)	0.4 (1.1)	0.8 (1.0)

#### *Course of anxiety and depression*

The descriptive results of anxiety and depression levels at the various assessment points are presented in Table 1. The correlation between anxiety and depression was 0.62 at  $T_1$ , 0.73 at  $T_2$  and 0.76 at  $T_3$ .

MANOVAs for repeated measures were performed separately for women and their partners in order to investigate the differences in the course of anxiety and depression between  $T_1$ ,  $T_2$  and  $T_3$ .

The results of the MANOVAs for women did not reveal any significant time effect for either anxiety or depression. However, a significant interaction effect for time x treatment outcome was indicated for anxiety ( $F(2,146)=6.5$ ;  $p<0.01$ ) and for depression ( $F(2,146)=12.9$ ;  $p<0.01$ ). In addition, there were significant effects for treatment outcome for both anxiety ( $F(2,146)=7.5$ ;  $p=0.01$ ) and depression ( $F(2,146)=16.1$ ;  $p<0.01$ ). Post hoc t-tests for non-pregnant women revealed a significant increase in both anxiety ( $t(64)=-2.5$ ;  $p=0.02$ ) and depression ( $t(64)=-2.9$ ;  $p=0.01$ ) between  $T_1$  and  $T_2$ , while pregnant women showed a decrease in anxiety ( $t(82)=3.2$ ;  $p<0.01$ ) and depression ( $t(82)=3.4$ ;  $p<0.01$ ) in the same period. Post hoc t-tests did not reveal any change in anxiety ( $t(64)=-0.74$ ;  $p=0.46$ ) or depression ( $t(64)=0.18$ ;  $p=0.86$ ) between  $T_2$  and  $T_3$  in non-pregnant women. The same was true for pregnant women.

The results of the MANOVAs for men did not reveal any significant time, interaction or treatment outcome effect for anxiety or any interaction and outcome effect for depression. They did reveal, however, a significant time effect for depression ( $F(2,69)=5.1$ ;  $p=0.01$ ). Post hoc t-tests for men after successful treatment revealed a significant decrease in depression ( $t(1,53)=2.7$ ;  $p=0.01$ ) between  $T_2$  and  $T_3$ . The post hoc t-tests did not reveal any other significant results.

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

Additional MANOVAs were performed for women whose treatment was not successful 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 one or two cycles versus three or more (interaction effect time x number of cycles:  $F(2,63)=1.06$ ;  $p=0.35$  for anxiety and  $F(2,63)=0.24$ ;  $p=0.78$  for depression; time effect:  $F(2,63)=0.02$ ;  $p=0.83$  for anxiety and  $F(2,63)=1.19$ ;  $p=0.28$  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  $F(2,63)=0.18$ ;  $p=0.83$ ; children  $F(2,63)=0.00$ ;  $p=0.96$ ) or depression (time x children  $F(2,63)=1.13$ ;  $p=0.33$ ; children  $F(2,63)=0.00$ ;  $p=0.99$ ).

*Subclinical forms of anxiety and depression*

At T<sub>1</sub>, 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 T<sub>2</sub> and 20% at T<sub>3</sub>. Six percent showed subclinical levels of anxiety at T<sub>2</sub> as well as at T<sub>3</sub>. With respect to subclinical forms of depression at T<sub>1</sub>, 12% of the women who did not get pregnant scored above the cut-off. This was 20% at T<sub>2</sub> and 25% at T<sub>3</sub>. Again, 6% showed subclinical levels of depression anxiety at T<sub>2</sub> as well as at T<sub>3</sub>. 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.

**Table 2.** Pearson correlation coefficients between predictors and change scores for anxiety and depression between T<sub>1</sub> and T<sub>3</sub>

	Total course (T <sub>1</sub> – T <sub>3</sub> )	
	Anxiety	Depression
Demographic		
age	0.08	0.15
educational level		
Clinical		
duration of infertility	-0.20	-0.17
Personality characteristics		
neuroticism	0.31*	0.47**
optimism	-0.22	-0.34**
Infertility-related cognitions		
helplessness	0.10	0.32*
acceptance	-0.17	-0.31**
Coping		
problem management	0.06	-0.01
emotional approach	0.22	0.11
cognitive avoidance	0.08	-0.15
Social support		
general marital dissatisfaction	0.30*	0.28*
sexual dissatisfaction	0.15	0.23
perceived social support	-0.37**	-0.34**

\*\* p<0.01; \*p<0.05

*Factors that contributed to the course of anxiety and depression after unsuccessful treatment*

In Table 2, correlations of change scores for anxiety and depression between T<sub>1</sub> and T<sub>3</sub> are presented with background variables and predictors. In predicting the change in anxiety from T<sub>1</sub> to T<sub>3</sub>, 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 3.

The results revealed that T<sub>1</sub> levels of anxiety (Delta R<sup>2</sup>=0.27; p<0.01), neuroticism (Delta R<sup>2</sup>=0.08; p<0.01) and perceived social support, together with general marital dissatisfaction (Delta R<sup>2</sup>=0.07; p<0.05) added significant additional variance in anxiety levels at T<sub>3</sub>. The model with these factors fully explained 42% of the variance in anxiety at T<sub>3</sub> (Delta R<sup>2</sup>=0.42; p<0.05).

**Table 3.** Intercorrelations for predictor variables

	1	2	3	4	5	6	7
1. neuroticism	--	-0.35**	0.31*	-0.34**	0.46**	0.21	-0.41**
2. optimism		--	-0.14	0.11	-0.39**	-0.08	0.06
3. helplessness			--	-0.60**	0.13	0.12	-0.19
4. acceptance				--	-0.09	-0.27*	0.30*
5. marital dissatisfaction					--	0.30*	-0.38**
6. sexual dissatisfaction						--	-0.20
7. perceived social support							--

\*\* p<0.01; \* p<0.05

In predicting depressed mood at T<sub>3</sub>, 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  $R^2=0.09$ ;  $p<0.05$ ), and personality characteristics (Delta  $R^2=0.22$ ;  $p<0.01$ ) added significant additional variance in depression levels at  $T_3$ . The model that explained the most variance (Delta  $R^2=0.36$ ;  $p<0.01$ ) 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**

After the final unsuccessful treatment cycle, women showed significantly higher levels of anxiety and depression than after a successful treatment cycle. There was no significant change in these anxiety and depression levels from the time just after the last unsuccessful cycle to six months later. At these two points in time, a substantial percentage of the women showed subclinical forms of anxiety ( $T_2$ : 23%;  $T_3$ : 20%) and depression ( $T_2$ : 20%;  $T_3$ : 25%). These results mean that anxiety and depression increased during one or more unsuccessful treatment cycles and that six months after the final cycle only limited signs of recovery could be identified.

After successful treatment, the result showed the opposite: a decrease in anxiety and depression from pretreatment assessments to the time just after the last treatment cycle, and no significant change in the six months after the last cycle. The percentage of women showing subclinical forms of depression also decreased in the period between pretreatment assessment and assessments just after the last cycle.

There was no significant change in anxiety and depression in men independent of treatment outcome. Only after successful treatment did men show a significant decrease in depression in the six months after the final cycle.

The present study showed that both anxiety and depression were important emotional responses in women, even half a year after the unsuccessful treatment. This is only partly in line with what was expected. We expected a more significant decline of anxiety in the period just after and six months after the final unsuccessful treatment cycle, because there would be an end to uncertainty about the treatment outcome and the threat of the treatment. This might be explained by continuation of uncertainties about infertility. Other studies have indicated that couples still consider or hope for new treatment possibilities for a considerable time after the end of treatment.



(van Balen et al., 1993; Leiblum et al., 1987). Nevertheless, the results seem to indicate that depression is the most apparent emotion six months after the last unsuccessful treatment cycle. The proportion of women showing subclinical forms of anxiety tends to decrease after the last treatment cycle, while the proportion of women with subclinical forms of depression tends to increase.

The prospective part of the study identified neuroticism and dissatisfaction with the marital relationship as risk factors and perceived social support as a protective factor for the development of both higher levels of anxiety and depression six months after the final treatment cycle. These factors explained the greatest variance in change for both anxiety and depression. 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 important aspect of negative affectivity or neuroticism (Clark et al., 1994). In addition, however, optimism and acceptance of fertility problems were protective factors, while helplessness was a risk factor in the development of only depression. This is in line with theories that assume low activity and lack of positive affect to be specific aspects of depression. However, the cognitive factors did not independently add significant variance to the change in depression. The lack of significant, additional explained variance might be partly due to the limited power of the study.

The effectiveness of coping partly depends on the characteristics of the stressor (Penley et al., 2002; Suls and Fletcher, 1985). 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-focussed coping are assumed to be ineffective. The results of the present study partly support this: no relationship was found between problem-focussed, 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 (Terry & Hynes, 1998). The negative relationship between cognitions of acceptance of fertility problems and increase in depression between  $T_1$  and  $T_3$  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. This might partly be due to the complexity of the stressor and the time lag between coping

assessment and emotional response. Effective coping depends on the characteristics of the stressor. In the present study, the stressor 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 & Mangan, 1983). Re-evaluation of the stressor seems to be important in the event of loss (Davis & 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.

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 partner is the most important source of social support (Laffont & Edelmann, 1994<sup>b</sup>). However, social interaction can also be a risk factor for the development of anxiety and depression when couples suffering from fertility problems receive unsupportive comments (Mindes et al., 2003).

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 especially 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 & Kaltman, 2001; Janssen et al., 1997).

A difficult aspect of the study was definition of the final treatment cycle. It seems hardly 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 about fifty percent of the women who have stopped fertility treatment would restart if there would be new treatment possibilities (Van Balen & 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 focussed on the meaning or the cognitions of fertility problems and on improving social support. Future studies will have to show whether these counselling efforts will prevent the development of severe emotional problems. However, the effectiveness of cognitive behavioural therapy in relieving emotional problems has already been shown in several other areas of behavioural medicine (Evers et al., 2002; Alloy et al., 1999).

## Chapter 7

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Satisfaction with the marital and sexual relationship in couples during and after IVF and ICSI treatment, a longitudinal study

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**SATISFACTION WITH THE MARITAL AND SEXUAL RELATIONSHIP IN COUPLES DURING AND AFTER IVF AND ICSI TREATMENT, A LONGITUDINAL STUDY.****Abstract**

The marital relationship is an important source of social support for women entering fertility treatment. A satisfactory marital relationship might therefore be a protective factor in the development of emotional problems as the result of unsuccessful fertility treatment. From this point of view, it is important to know the impact of one or more unsuccessful fertility treatment cycles on the satisfaction with the marital relationship. In order to find this out, we investigated the course of satisfaction with the marital and sexual relationship in couples from the time of starting fertility treatment to six months after the last treatment cycle, and we investigated differences in this course with respect to gender, treatment outcome and cause of fertility problems. A design with repeated measures was used. Both women and their partners completed self-report questionnaires on marital and sexual dissatisfaction before starting the first In vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) treatment cycle, six weeks after the last cycle and six months after the last treatment cycle. The study took place in the outpatients clinic of the fertility department of the University Hospital Nijmegen. Eighty-six women and their partner starting the first cycle of an IVF or ICSI treatment participated in the study. The main outcome measures were dissatisfaction with marital and sexual relationship. The results indicated that the course of the marital dissatisfaction in women, differed significantly in accordance with treatment outcome. After unsuccessful treatment, there was a trend towards an increase in dissatisfaction, after successful treatment, there was a trend of a decrease. After an unsuccessful and after a successful treatment cycle, both men and women displayed an increase in sexual dissatisfaction six months after the last treatment.

Results suggest that unsuccessful infertility treatment has a slightly negative effect on the marital and sexual relationship of couples involved. After both successful and unsuccessful treatment there was an increase in sexual dissatisfaction. Increase of sexual dissatisfaction in couples after successful treatment might be due to symptoms of early pregnancy.

## Introduction

Fertility problems affect both women's and men's plans to start a family. Although only the woman is involved in most treatments, both men and women consider the fertility problems the worst thing that has ever happened to them (Mahlstedt, 1985). Several clinical studies on couples with fertility problems have already reported the impact of these problems on the couples' marital and sexual relationship (Diamond et al., 1999; Leiblum et al., 1998; Mennings, 1980), e.g. feelings of guilt, difficulties in communicating with each other about fertility problems, differences in motivation for further treatment, pressure from the social network and feelings of diminished sexual esteem.

Information about the marital and sexual relationship in couples facing fertility problems is important, because the marital relationship could be an important source of social support. At times when confronting a severe stressor, such as fertility treatment, a good marital relationship can buffer the effects of the fertility problems on well-being (Valentiner et al., 1994). Dissatisfaction increases couples' vulnerability to developing more severe emotional problems as a result of their fertility problems. Information about the course of the marital and sexual relationship may also provide a lead for counseling couples facing fertility problems.

There is a lack of empirical studies into the course of satisfaction with the marital and sexual relationship during and after consecutive fertility treatment cycles. Information about the course of satisfaction with the marital relationship at different treatment phases is scarce and is based on just one study exclusively involving women. This study did not show any difference in marital dissatisfaction after one unsuccessful treatment cycle, compared to pretreatment levels (Visser et al., 1994).

The only information about the course of satisfaction with the sexual relationship is based on a cross-sectional study in which couples with a relatively short duration of fertility problems have shown greater satisfaction with their sexual relationship than couples with a longer duration of fertility problems (Berg & Wilson, 1991).

Empirical studies into the course of satisfaction with the marital and sexual relationship after fertility treatment are lacking. Accordingly, the course of satisfaction after the last treatment is unclear, as is the question of whether there are differences in satisfaction in relation to treatment outcome.

The aim of the present study was to investigate the course of satisfaction with the marital and sexual relationship in both women and men from the

moment they start IVF or ICSI treatment till six months after the last treatment cycle. In addition, it was intended to investigate differences in this course with respect to gender, treatment outcome and cause of fertility problems. Assessment of satisfaction with the marital and sexual relationship took place at pretreatment, after the last IVF or ICSI treatment cycle, and six months after the last treatment cycle.

## **Method**

### *Participants*

Participants were recruited at a university hospital, located in a medium-sized city in the Netherlands. Complete data sets of all three measurements were received from 86 consecutive couples<sup>1</sup>.

### *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 ( $T_1$ ), four weeks after the pregnancy test subsequent to the last treatment cycle ( $T_2$ ) and six months after the last treatment ( $T_3$ ). A cycle was defined as a last cycle when couples did not start further treatment in one year subsequent to the previous cycle. Marital and sexual dissatisfaction were assessed at  $T_1$ ,  $T_2$  and  $T_3$ . The average time between  $T_1$  and  $T_3$  was 16 months.

### *Procedure*

Women were asked to participate in the study when they visited the hospital for an intake interview with their physician prior to their first IVF or ICSI treatment. A long protocol with Decapeptyl® and Puregon® was used. After obtaining written informed consent, questionnaires were sent to their homes. Participants were asked to complete the questionnaires independently before the start of medication, and return them to the hospital in a prepaid envelop. Four weeks after the pregnancy test, a second questionnaire was sent by post, this was repeated after each consecutive cycle. Only data before the first ( $T_1$ ) and after the last cycle ( $T_2$ ) were taken into account. A last questionnaire followed six months after the last treatment cycle ( $T_3$ ). The procedure used in the second and third measurement points was the same as was used during the first.

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<sup>1</sup> Missing values of 15 men on  $T_2$  were replaced by the  $T_1$  score.



The study was approved of by the ethical committee of research with human beings of the hospital.

### *Measures*

Demographic (age and educational level) and gynaecological (duration and cause of the fertility problems) background characteristics were assessed with a self report questionnaire. Satisfaction with the marital relationship was measured with the Maudsley Marital Questionnaire (Arrindell et al., 1983). Respondents were asked to report their satisfaction on a 9-point scale. Higher scores are an indication of greater dissatisfaction. Two scales of the MMQ were used: marital satisfaction (10 items, range 0 [no dissatisfaction] to 80 [high levels of dissatisfaction]) and sexual satisfaction (5 items, scores ranging from 0-40, representing low and high levels of dissatisfaction, respectively). Alpha was 0.85 for marital satisfaction and 0.70 for sexual satisfaction. The following items are some examples in the marital satisfaction scale: Is your partner attractive to you? Do you receive enough warmth from your partner? Does your partner assume his/her responsibility for your relationship? How many times have you considered separating from your partner? Do you feel in any way inhibited in bringing up the subject you want with your partner? The five items of the sexual satisfaction scale are as follows: Are you satisfied with the amount of sexual intercourse you had last month? How many times did you have intercourse with your partner last month? How satisfied are you with the number of times you have sex with each other? How often do you have an orgasm during sexual contact with your partner? Do you enjoy sex with your partner?

### *Statistical analyses*

MANOVAs with repeated measures and post hoc ONEWAY analyses of variance were performed to examine differences in course of marital and sexual dissatisfaction between pregnant and non-pregnant participants. Analyses were carried out separately for women and men.

### **Results**

Mean age of the women was 34.3 years (range=25-42) and of the men 36.8 years (range=29-55). The educational level was low for 31% of the women, moderate for 41% and high for 28%. Mean duration of fertility problems was 5 years (range=0-13). The causes of the fertility problems

were female causes (19%), male causes (47%), both female and male causes (9%) and idiopathic causes (25%). Sixty-five (76%) of the women became pregnant after the treatment, while 21 did not.

The descriptive results of the marital and sexual satisfaction of both women and men at three different measurement points are provided in Table 1.

**Table 1.** Dissatisfaction with marital and sexual relationship for women and men before and after successful (N = 65) and unsuccessful treatment (N=21); SD between parentheses

	Marital dissatisfaction			Sexual dissatisfaction		
	T <sub>1</sub> <sup>a</sup>	T <sub>2</sub> <sup>b</sup>	T <sub>3</sub> <sup>c</sup>	T <sub>1</sub> <sup>a</sup>	T <sub>2</sub> <sup>b</sup>	T <sub>3</sub> <sup>c</sup>
<b>Women</b>						
Successful treatment	9.8 (6.5)	9.8 (6.4)	8.6 (6.6)	8.2 (6.0)	10.7 (7.0)	13.6 (6.6)
Unsuccessful treatment	7.7 (5.4)	9.1 (6.9)	11.1 (8.8)	5.5 (4.6)	4.8 (6.5)	9.9 (9.5)
<b>Men</b>						
Successful treatment	8.8 (5.0)	8.9 (5.1)	8.3 (5.1)	7.2 (6.4)	10.2 (7.0)	13.2 (8.0)
Unsuccessful treatment	7.2 (6.3)	6.3 (7.0)	7.6 (5.0)	6.4 (6.6)	6.1 (7.6)	8.9 (7.4)

<sup>a</sup> T<sub>1</sub>: before the first treatment cycle

<sup>b</sup> T<sub>2</sub>: after the first treatment cycle

<sup>c</sup> T<sub>3</sub>: 6 months after the last treatment cycle

MANOVAs with repeated measures were performed separately for women and men. With respect to marital dissatisfaction in women, there was no main effect for time and treatment outcome. However, the interaction between time and treatment outcome was significant ( $F(1,85)=3.51$ ;  $p=0.03$ ). Post hoc t-tests revealed the trend of an increase in dissatisfaction between pretreatment and follow-up assessments after consecutive unsuccessful treatments ( $t(20)=-1.89$ ;  $p=0.07$ ) and the trend of a decrease in dissatisfaction after a successful treatment ( $t(64)=1.73$ ;  $p=0.09$ ).

The results with respect to the course of the sexual relationship in women showed a different pattern. There was a main effect of time ( $F(2,84)=17.89$ ;  $p<0.01$ ) and treatment outcome ( $F(2,84)=9.41$ ;  $p<0.01$ ), and no significant interaction effect. Post hoc t-tests revealed an increase in sexual

dissatisfaction after both unsuccessful ( $t(20) = -3.06$ ;  $p = 0.01$ ) and successful treatments ( $t(64) = -5.88$ ;  $p < 0.01$ ).

MANOVAs for repeated measures on the course of marital satisfaction in men did not reveal any significant time, treatment outcome or interaction effect. Analyses for the course of sexual satisfaction in men revealed a significant time effect ( $F(2,84) = 11.21$ ;  $p < 0.01$ ), and outcome effect ( $F(2,84) = 4.47$ ;  $p = 0.04$ ) and no interaction effect. Post hoc t-tests indicated an increase in sexual dissatisfaction in men after a successful treatment ( $t(64) = -6.62$   $p < 0.01$ ) and no significant change in dissatisfaction after an unsuccessful treatment.

ONEWAY analyses for differences in marital and sexual satisfaction with respect to cause of the fertility problems did not reveal any cause effect in women or men.

In women, explorative MANOVAs were performed to investigate the nature of the course of sexual dissatisfaction at item level. Accordingly, the courses of scores on the five items of the sexual satisfaction scale were analyzed separately. These analyses indicated a significant decrease in frequency of coitus in both pregnant and non-pregnant women (time effect:  $F(2,84) = 18.71$ ;  $p < 0.01$ ), the decrease in pregnant women being the most apparent (time x outcome effect:  $F(2,84) = 3.12$ ;  $p = 0.47$ ). In addition, dissatisfaction with the frequency of coitus increased in both pregnant and non-pregnant women (time effect:  $F(2,84) = 5.23$ ;  $p = 0.01$ ). Sexual enjoyment remained the same in pregnant women but decreased in non-pregnant women (time x outcome:  $F(2,84) = 7.75$ ;  $p < 0.01$ ).

## **Discussion**

This study indicated a difference in course of dissatisfaction with the marital relationship between pregnant and non-pregnant women: a trend towards an increase in dissatisfaction after unsuccessful treatment and a trend towards a decrease after successful treatment. After the unsuccessful treatment, there was a significant increase in dissatisfaction with the sexual relationship in women from pretreatment levels to six months after the last treatment cycle. In addition, six months after the successful treatment, a significant increase in dissatisfaction with the sexual relationship was identified for both women and men.

There was no significant change in dissatisfaction with the marital relationship in women from pretreatment to posttreatment levels but the

trend was towards an increase ( $p=0.07$ ). Satisfaction levels are still within normal levels. It seems as if the marital relationship in most couples was strong enough to handle the stress of fertility problems. This is of interest because the marital relationship is an important source of support for couples facing fertility problems (Laffont & Edelmann, 1994). The availability of this support can buffer the negative effects of fertility problems on distress levels for both partners (Valentiner et al., 1994). Six months after the last unsuccessful treatment, most couples will be in the 'resolution phase', in which couples stop medical treatment, mourn the loss of their dreams of having their own child and refocus on a life without children or with adopted children (Diamond et al., 1999). The study by Leiblum et al. (1998) pointed out that three to ten years after the last artificial reproductive treatment, differences in marital and sexual dissatisfaction could not be reported between women with and without children. In line with this result, we may assume that the resolution phase will result in a refocusing on life without children and that dissatisfaction levels reported six months after the last treatment will not increase within several years. However, longitudinal studies will have to find support for this assumption.

Pregnant women and their partners showed no significant change in marital dissatisfaction from pretreatment to posttreatment levels, but they both showed a significant increase in sexual dissatisfaction. The increase in sexual dissatisfaction in women corresponds with other studies on sexual satisfaction in pregnant women. This increase might be partly due to a decrease in interest in women in sexual intercourse (VonSydow et al. 2001; Brancroft, 1989). There are, to our knowledge, no studies that have compared the sexual interest of pregnant women with and without a history of fertility problems. However, it is generally assumed that women might be afraid that sexual activities could negatively affect their pregnancy after IVF or ICSI. This means that the increase in sexual dissatisfaction of these women might be more apparent than in pregnant women without fertility problems.

The results of the present study do not provide information about possible differences in the reasons for sexual dissatisfaction in pregnant and non-pregnant couples. The increase in dissatisfaction in the pregnant group may be due to a decreased interest in sexual intercourse, while the increase in non-pregnant women could be due to a diminution of intimacy as a whole. This assumption is supported by the decrease in marital

satisfaction in non-pregnant women, which is absent in pregnant women. In addition, explorative analyses of differences in satisfaction in the pregnant and non-pregnant groups at item level supported these assumptions.

With respect to gender differences in the course of marital and sexual dissatisfaction, the results of the present study showed the same picture as for differences in the course of dissatisfaction during one unsuccessful treatment cycle (Boivin et al., 1996). It seems as if the comparable course between men and women during one treatment cycle continues after several consecutive cycles.

In the present study, no relationship was found between cause of the fertility problems and marital or sexual dissatisfaction. Both women and men appear to consider the fertility problems an issue that affects both of them, irrespective of the question who is the biological cause (Pasch, 2001).

A striking result of the present study is the higher pretreatment levels of sexual dissatisfaction in women who will become pregnant compared to those who will not. These results have to be cautiously considered because of the limited number of non pregnant women in the sample. However, the results could point towards the possibility of a higher incidence of sexual problems as the cause of fertility problems in the group of women that will become pregnant. Indeed, some studies assumed sexual problems to be a factor in the etiology of fertility problems in a subsample of couples (Fagan et al., 1986, Freeman et al., 1985). Because of the possible absence of other factors that determine fertility problems, there might be a high success-rate for these couples' in the IVF or ICSI treatment. This study, however, cannot draw any conclusion with respect to this point. Further research is needed to investigate sexual problems as one of the causes of fertility problems.

A limitation of the study is the lack of information about specific interaction patterns within couples. Comparisons between perceived, received and provided support between couples (mutual validation) have been shown to be the best distinction between couples that are satisfied or dissatisfied with their marital relationship (Abbey et al., 1995). More knowledge about interaction patterns might provide leads for supporting couples in dealing with marital conflicts during and after fertility treatment.

Another limitation is the definition of the last treatment cycle. We cannot exclude that couples have started other treatment cycles or have looked for further treatment possibilities one year after their last cycle. A last treatment

cycle is only definitively the last when the woman reaches the menopause (Diamond et al., 1999). The only possibility to counter this limitation is to keep studying these couples until their forties and fifties. Only then, the longer term course of satisfaction with marital and sexual relationship after unsuccessful IVF- or ICSI-treatment will get clear.

The results of the present study suggest that unsuccessful infertility treatment has little short term negative effect on satisfaction with the marital relationship in couples involved. However, after both successful and unsuccessful treatments, men and women showed an increase in dissatisfaction with their sexual relationship. Longitudinal studies into the course of marital and sexual dissatisfaction after successful and unsuccessful treatment is warranted in order to gain insight into the long term effects of fertility problems on the quality of the marital and sexual relationship.



## **Summary and Discussion**

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## SUMMARY AND DISCUSSION

In this thesis, we studied the emotional impact of unsuccessful IVF and ICSI treatment in women. These treatments frequently consist of several cycles of ovarian stimulation, egg-collection and embryo transfer, and the emotional response was expected to change during the course of one or more unsuccessful treatment cycles. We addressed the course of the emotional response (in terms of anxiety and depression) from pretreatment to six months after the last treatment cycle, as well as the factors that determined this course. The first part of the thesis focussed on the emotional response to one treatment cycle (short term emotional response) and possible differences in response with respect to treatment type and treatment outcome. The second part addressed the stress vulnerability factors that contribute to this short term emotional response. The third part of the thesis focussed on the long term emotional response to IVF and ICSI treatment six months after the last treatment cycle and on factors that contributed to that course. Based on these studies, we could identify possible risk and protective elements in the establishment of anxiety and depression as the consequence of unsuccessful treatment. Finally, we focussed on the long term course of satisfaction with the marital and sexual relationship.

### **Part 1. Short term course of anxiety, depression and satisfaction with the marital and sexual relationship**

In *Chapter 2*, it was shown that pretreatment levels of distress and satisfaction with the marital relationship did not deviate from age and gender-matched norm groups. Comparing IVF and ICSI patients with norm groups, previous studies revealed equivocal results. Some studies reported higher levels of distress (Salvatore et al., 2001; Oddens et al., 1999; Slade et al., 1997; Beaurepaire et al., 1994; Visser et al., 1994; Cook et al., 1989), while others did not find any differences (Henning & Strauss, 2002; Sanders & Bruce, 1999; Edelman et al., 1994; Hearn et al., 1987). In addition to differences in assessment methods (use of non standardised questionnaires, lack of comparison with age and gender-matched control groups), equivocal findings may be due to the number of previous treatment cycles and the length of time before the start of treatment. In the present study, women who started the first cycle of IVF or ICSI treatment

within a few days did not differ from norm groups in levels of distress and dissatisfaction with the marital relationship: indicating that women who undergo IVF or ICSI are not more distressed than the general population when they start treatment. However, the results cannot be generalized to the entire population of women facing fertility problems. The stress accompanying the threat of infertility can be tempered by the women's high expectations about the chances of success of treatment, particularly at the start of the first cycle. Accordingly, they might be eager to take action to solve their fertility problems. This may lead to an increase in optimism about the outcome and enhanced perceived control, resulting in decreased distress.

The results also indicated higher pretreatment levels of depression in women who did not get pregnant in the first treatment cycle. This suggests a possible relationship between pretreatment depression and the chances of pregnancy. This issue of the relationship between psychological factors and the success rate of fertility treatment has been further elaborated in another study based on the same sample and is therefore not further explored in this thesis (see Smeenk et al., 2001).

Results with respect to the short term course of the emotional response to the treatment, as described in *Chapters 2 and 3*, indicated a significant increase in both anxiety and depression after the first unsuccessful treatment cycle, while anxiety and depression decreased in pregnant women. These results support findings of previous studies, which indicated an increase in distress after an unsuccessful treatment cycle (Slade et al., 1997; Connolly et al., 1992; Litt et al., 1992; Newton et al., 1990) and were in line with our hypothesis that both anxiety and depression would increase after the first unsuccessful cycle. The first unsuccessful cycle already elicited feelings of depression, even when there are other treatment possibilities. This might be a response to the experience of loss and loss of hope that seems already apparent at the end of the first unsuccessful treatment cycle. In addition, the percentage of women who met the criteria for subclinically relevant forms of depression increased from 11% before the start of the treatment to 21% after the first unsuccessful cycle.

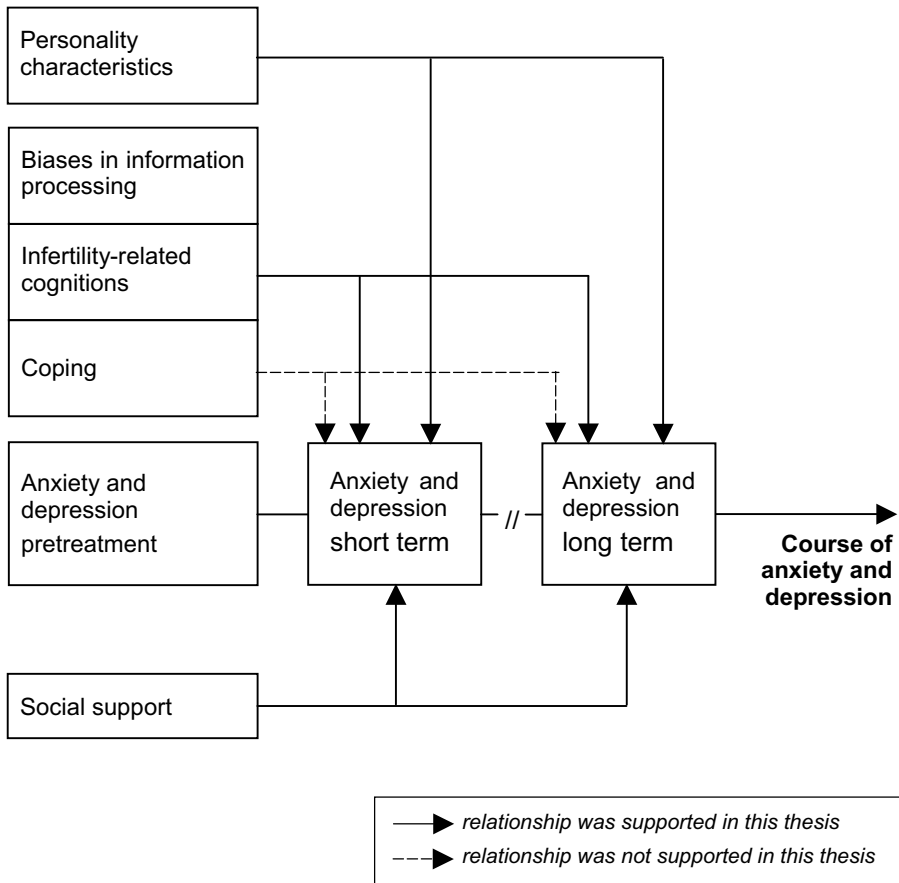
Irrespective of treatment outcome, women did not show any short term change in marital satisfaction. This is in line with the scarce longitudinal studies on this issue (Visser et al., 1994; Connolly et al., 1990). However, again irrespective of the outcome of the first treatment cycle, dissatisfaction with the sexual relationship increased. Increase in dissatisfaction with the

sexual relationship in pregnant women may be due to less interest in sexual intercourse, which is not uncommon during pregnancy (Brancroft, 1989), while the reasons for the increase in dissatisfaction with the sexual relationship in the non-pregnant women may be a consequence of increased depression and a lack of spontaneous sexual behaviour as the result of compelling treatment schedules.

Another issue, addressed in *Chapter 3*, was the possible change in pretreatment intentions for further treatment in the event of an unsuccessful first cycle. Before the start of treatment, a vast majority of the women (82%) intended to continue further treatment in the event of failure, while only 65% actually continued treatment after the first unsuccessful cycle. Prior to treatment, the women who ceased treatment already showed higher levels of anxiety and depression than the women who continued treatment, which suggests that the stress of treatment leads to higher cessation rates after one unsuccessful cycle for women distressed at pretreatment than for women less distressed at pretreatment.

## **Part 2. Factors that contribute to the short term course of anxiety and depression**

Part two of the thesis addressed factors that contributed to the course of anxiety and depression after the first unsuccessful treatment cycle in women. Based on stress vulnerability models (Alloy et al., 1999; Beck & Clark, 1997; Holahan et al., 1996; Williams et al., 1996; Watson & Clark, 1984), a comprehensive set of factors was taken into account. *Chapter 4* focussed on two possible contributors to the short term course of anxiety: neuroticism and biases in information processing. Neuroticism, or negative affectivity, defined as an enhanced reactivity to threatening information, is assumed to be a general, dispositional risk factor for the development of both anxiety and depression. In addition, cognitive theories on information processing maintain that preattentive biases towards threatening information are important factors in the development of anxiety. The study demonstrated that preattentive biases toward threatening information at pretreatment contributed to the short term course of anxiety in women after an unsuccessful cycle. This is in line with the scarce empirical studies, showing that preattentive biases towards threat predicted changes in anxiety after a severe stressor in nonclinical samples (Pury, 2002; MacLeod & Hagan, 1992). The study in the present thesis also showed that



**Figure 1.** Factors that contributed to the short and long term course of anxiety and depression

preattentive biases towards stressor-related threat contributed to anxiety, even when controlling for neuroticism. This effect was especially prominent in a subsample showing an increase in anxiety as the result of unsuccessful treatment, supporting the assumption that a preattentive bias toward stress may become especially apparent under conditions of high stress (Mogg & Bradley, 1998; Williams et al., 1996). Summing up, the results indicated that vulnerability to anxiety seems to be apparent on both

automatic (preattentive bias) and strategic (neuroticism) levels of information processing. Thus, according to the model proposed in the introduction to this thesis, support was found for the relationship of both neuroticism and biases in information processing to the short term anxiety response (see Figure 1).

In *Chapter 5*, the strategic factors contributing to the short term course of anxiety and depression were investigated. Four groups of factors were supposed to predict the emotional response to the first unsuccessful treatment cycle: personality characteristics (neuroticism, optimism and extraversion), fertility-related cognitions (helplessness and acceptance), coping strategies (active problem solving and avoidance), and general (perceived social support and size of social network) and specific (marital and sexual dissatisfaction) aspects of social support. Results indicated that neuroticism, cognitions of helplessness, less acceptance of the fertility problems and dissatisfaction with the marital relationship contributed to an increase in anxiety and depression after the first unsuccessful treatment cycle. Less perceived support contributed to an increase in anxiety. To sum up, in addition to neuroticism, cognitions of fertility problems and social support are important contributors to the course of both anxiety and depression after an unsuccessful treatment cycle (see Figure 1).

The importance of neuroticism as a contributor to the emotional response to a severe stressor is well recognised (Clark et al., 1994; Hotart et al., 1989) and was supported in this thesis with regard to the stressor of the first unsuccessful IVF or ICSI treatment. With regard to fertility-related cognitions, it was proposed that particular helplessness would be most closely related to the course of depression. Although cognitions of helplessness also contributed to the course of anxiety, this contributed more to the course of depression than to that of anxiety, supporting the prominent role of helplessness in establishing depression in various populations (Evers et al., 2001; Seligman, 1975). Cognitions of acceptance of the fertility problems contributed to a less negative course of both anxiety and depression. This is in line with a previous study that found acceptance of fertility problems to be a protective factor in the emotional response to an unsuccessful treatment cycle (Terry & Hynes, 1998). This also corresponds with other studies showing the beneficial function of acceptance as a reaction to uncontrollable long term stressors, suggesting that subjects who acknowledge the long term stressor and simultaneously perceive the ability

to live with and master the consequences of the stressor suffer less distress (Evers et al., 2001).

Coping factors did not contribute to the short term course of anxiety and depression. The fact that our coping factors assessed at pretreatment did not contribute to the course of either anxiety or depression after an unsuccessful cycle may be due to the time lag and the occurrence of several important treatment events between pretreatment coping assessment and the emotional response after the first cycle. Unsuccessful treatment has several aspects that may require different and specific coping strategies: the threat of treatment, the uncertainty of the outcome, the unpredictability of the course of the treatment, and the loss of hope for pregnancy. The coping strategies measured in the present study might have been too general to identify different coping strategies for different treatment-related stressors.

The hypothesised role of social support as a protective factor in the emotional response to an unsuccessful treatment cycle was supported. Specific factors of social support, related to the partner relationship, i.e. satisfaction with the marital relationship as well as more general aspects of perceived social support, were shown to be protective factors in the emotional response to unsuccessful treatment, underlying the importance of partner-related and broader aspects of social support for increased distress after unsuccessful fertility treatment.

### **Part 3. The long term course of anxiety, depression and satisfaction with the marital and sexual relationship, and factors that contribute to that course**

The long term emotional response to IVF and ICSI treatment is described in *Chapter 6*. Results revealed an increase in anxiety and depression in non-pregnant women between pretreatment assessments and assessments just after the last treatment cycle, while no significant differences were found between the assessments just after the last cycle and six months later. This means that no signs of recovery could be identified in non-pregnant women in the six months after the last treatment cycle. In contrast to this, pregnant women showed a decrease in both anxiety and depression in the same period.

When we compare the observed long term emotional response to the unsuccessful treatment with the hypothesised course (see Figure 1 in

chapter 1) the results of the present study only partly supported our hypotheses. In line with expectations, a significant increase in both anxiety and depression was found after consecutive unsuccessful cycles. However, anxiety and depression did not significantly decrease in the six months after the last cycle. Anxiety levels would be expected to decline, because the treatment was completed and the outcome was clear. It is possible that the lack of decline of anxiety may be attributed to the continuation of considering further treatment possibilities. Previous studies have pointed out that couples still consider possibilities for further treatment even three years after ceasing treatment, (Leiblum et al., 1998; Van Balen & Trimbos-Kemper, 1993). Accordingly, it is possible that most couples did not feel their fertility treatment was finished even six months after the last cycle. The fertility treatment issue will probably remain unsolved and under consideration, and the threat of possible further treatment and worry about the uncertainty of the outcome will continue to exist in their minds. Likewise, the expected slight decline of depression was not observed in the study. There was no significant change in depression in the six months after the ceasing treatment. Previous studies on adjustment to other forms of loss (e.g. due to loss of a partner, miscarriage or perinatal loss) indicated signs of recovery half a year afterwards, suggesting that distress levels would decline after another six months (Bonanno & Kaltman, 2001; Janssen et al., 1996). However, loss of hope of a pregnancy implies the loss of an ideal, of something that has yet to come about. There are no rituals such as funerals to work through that kind of loss (Strauss, 2002, Van Eck, 1997; Rehner, 1989). Moreover, there is no tangible loss in the sense that someone is lost who was part of daily life, which may possibly leading to complicating factors in the decline of distress.

Although our data has indicated that the majority of the women adjusted well to the failure of the treatment, a considerable group of women showed subclinical forms of depression and anxiety. Before the first treatment cycle, 11% - 12% of the women scored above the cut-off for sub clinically relevant forms of anxiety and depression. Just after the last unsuccessful cycle, 24% of the women scored above subclinical cut-offs for anxiety and 20% for depression. Six months after the last unsuccessful treatment cycle, 20% of the women still showed subclinical forms of anxiety, while 25% showed subclinical forms of depression. These women could be at risk of developing more severe forms of depression in the near future (Howarth et al., 1994). The percentage of women in our study showing subclinical forms



of anxiety and depression is somewhat higher than that reported in other studies (Connolly et al., 1992; Newton et al., 1990), which may be due to the accumulation of emotional response through consecutive unsuccessful treatment cycles.

Furthermore, we studied factors in chapter 6 that contributed to the course of anxiety and depression between pretreatment and six months after the last treatment cycle. The same set of strategic factors assumed to contribute to the short term emotional response (see chapter 5) was used to investigate their contribution to the long term emotional response.

Results indicated that more neuroticism and dissatisfaction with the marital relationship contributed to an increase in both anxiety and depression between pretreatment and six months after the last unsuccessful treatment cycle. More helplessness only contributed to an increase of depression. In addition, less optimism and acceptance of the fertility problems contributed to an increase in depression too, while less perceived social support contributed to an increase in anxiety. The results supported the central role of neuroticism or negative affectivity in the development of both anxiety and depression. Support was also found for the additional importance of cognitions of fertility problems in establishing depression and the role of social support characteristics for establishing both anxiety and depression (see Figure 1).

Results indicate that there are similar factors that contribute to the short and long term emotional response. This provides an opportunity to identify groups of women at risk for the development of severe emotional problems as the result of unsuccessful treatment. Accordingly, the factors identified might be used for developing a screening instrument for identifying groups of women at risk for heightened distress at pretreatment and developing tailored psychological interventions for these women at risk.

To gain insight into the effect of IVF and ICSI treatment on the marital and sexual relationship, we described the long term course of women's dissatisfaction with the marital and sexual relationship in *Chapter 7*. The results did not indicate any changes in the long term course of dissatisfaction with the marital relationship, neither in pregnant nor non-pregnant women. This suggests that most relationships could withstand the stress of the treatment, even when it did not result in pregnancy. However, there was a substantial decrease in women's sexual satisfaction after both a successful and an unsuccessful treatment at the six-month follow-up. The increase after a successful treatment might be due to the fact that women

are less interested in sexual intercourse during pregnancy, especially IVF and ICSI pregnancies (VonSydow et al., 2001). However, increase in sexual dissatisfaction after unsuccessful treatment could be due to reduced enjoyment of the sexual relationship because of the stress of the treatment and the couples' search for a new form of sexual relationship independent of the focus on conception. Anyhow, it may be of clinical importance to prepare couples for the possible negative effects of the treatment on their sexual relationship.

### **Men's emotional response**

The present thesis focussed on women's emotional response to unsuccessful treatment. Men's responses were taken into account exploratively. Several studies on emotional aspects of IVF and ICSI treatment have reported men as having less emotional response to fertility problems than their female partners (Henning & Strauss, 2002; Berg et al., 1991). In contrast to these results, men show the same stress as women when describing the emotional stress of fertility problems (Boivin et al., 1996). In line with previous studies, the results of the thesis revealed a negative emotional response in women and hardly any changes in the emotional status of men. This supports the reduced emotional impact of fertility treatment and its failure in men, compared with their partners. Although the stress of the threatening infertility seems to be high in men (Boivin et al., 1996), this did not affect emotional well-being in men. Further research is warranted in order to shed more light on the issue of men's reaction to infertility and fertility treatment.

### **The emotional response to successful treatment**

Successful IVF and ICSI treatment seems to alleviate emotional distress. Women's results show a decline in anxiety and depression shortly after successful treatment. Immediately following a successful treatment cycle, levels of anxiety and depression are already below pretreatment levels. Since pretreatment levels of anxiety and depression were comparable to norm groups, pregnant women showed distress levels even below the norm. The results indicated that stress related to treatment declined in the event of success. This suggests that increased distress in women after

unsuccessful treatment is not due to the treatment itself but rather to the stress of the threat of infertility.

### **Limitations of the study**

The study has some limitations that must be discussed. First of all, there was relatively high attrition (drop out of the study) at the various measurement points. Closer analyses revealed no selective attrition with respect to baseline levels of anxiety, depression, marital and sexual satisfaction, however selective attrition occurred after an unsuccessful treatment cycle, which means that pregnant women and their partners were over-represented in the sample. Attrition after unsuccessful treatment was especially high in women who ceased treatment after one or two cycles. These women were characterised by higher distress at pretreatment. Selective attrition implies that the results might not be generalised to women who ceased treatment after one cycle. Due to attrition, the power of the study to test a fully comprehensive model for factors contributing to the short and long term course of the emotional response was limited.

Another limitation is the definition of the last treatment cycle. It is possible that a group of non-pregnant women in our follow-up sample still consider further treatment possibilities in the near future. The difficulty of assessing the emotional response to definitive unsuccessful treatment is evidenced by the fact that treatment possibilities continue to increase, which may stimulate consideration of these possibilities and hope in women, even after the point where IVF or ICSI treatment seems finished. This implies that the present study did not investigate emotional response after the definitive end of treatment. Ongoing consideration of further treatment could explain enhanced levels of anxiety, even six months after the last cycle. However, the mourning process cannot actually start until women have definitively abandoned their attempts to become pregnant. Accordingly, depression levels six months after the last cycle could even be higher if only women were reckoned with who had actually and definitively rejected the possibility of other treatments.

### **Future research**

The present study revealed that a considerable percentage of women still showed subclinical forms of anxiety and depression six months after the

last treatment cycle. Longitudinal studies with assessments in the first years after ending treatment will have to show whether these increased levels of emotional distress can be understood as part of an adjustment process and will accordingly return to normal within two years, as shown by other studies on adjustment to loss (Bennano & Kaltman, 2001, Janssen et al., 1996), or whether they are indications of a more complicated adjustment process, due to the special characteristics of the emotional stress of threatening infertility. If the latter suggestion is the case, this will have implications for clinical practice since these women might benefit from additional psychological interventions.

Another interesting aspect for further research is the occurrence of positive emotions (as assessed by the vigour scale of the Profile of Mood Scale (McNair et al., 1971) in terms of active, bright, vivacious, lively) following one or more unsuccessful treatments. Positive and negative responses to a severe stressor have been shown to be partly independent (Watson & Tellegen, 1985). The present study focussed on the negative emotional response, but this negative response could possibly be accompanied by a positive response due to the development of other life goals in place of having children. In this case, the relationship between acceptance and positive mood would be interesting.

In addition, future studies will have to incorporate investigations into factors that have contributed to the course of satisfaction with the marital relationship. Factors that have been shown to play a role in the emotional response to a severe stressor in women might not automatically be as important in the course of the satisfaction with the marital relationship. This is an important issue because of the protective role of a satisfying marital relationship in the emotional response to unsuccessful treatment.

Following the results of the present study, based on a comprehensive set of risk factors for problematic emotional response to unsuccessful treatment, a short questionnaire can be developed. The investigation of the predictive value of this type of short inventory for the emotional response to one unsuccessful treatment cycle is already in progress. Based on this kind of inventory, further research can be carried out on the effects of tailored psychological interventions for women at risk of developing severe emotional problems as the result of unsuccessful treatment.

**Clinical implications**

The present study revealed that most women could effectively deal with the stress of IVF or ICSI treatment and of infertility. Nevertheless, about a quarter of the women still showed subclinical forms of emotional distress six months after the last treatment cycle. These women may be at risk of developing serious emotional problems over time and might benefit from psychological interventions to support them in the process of coming to terms with 'definitive' infertility. The treatment itself did not seem to be the most important stressor. The decrease in distress in pregnant women immediately after the treatment cycle indicated that women adjusted well to the treatment stressor. The result of the treatment has been shown to be the most important factor. The threat of infertility seemed to evoke the most negative emotional response. The present thesis showed neuroticism to be an important contributor to the emotional response to unsuccessful treatment. As a dispositional, relatively stable factor, neuroticism is not sensitive to change. However, the present thesis also indicated the importance of cognitions of fertility problems and of social support as contributors to the emotional response to treatment. Accordingly, the evaluation of life without children, the consequences for relationships with the partner, family and friends are important points of departure for psychological interventions.

Fertility professionals can stimulate the process of acceptance of fertility problems and communications about fertility problems in couples by discussing these issues with their patients (Boivin & Kertenich, 2002; Kertenich et al., 2002;) and by asking about such things as possible plans in the event of unsuccessful treatment and possible differences in motivation for treatment between women and men. In addition, clinicians can prepare patients for possible emotional reactions to unsuccessful treatment. Enhanced distress can be a natural reaction to unsuccessful treatment. Couples indicated a need for information on emotional aspects of fertility problems (Hammarberg et al., 2001). This preparatory information in forms of psychosocial education might enhance couples feeling of control over their emotional response to treatment failure. It might reassure them that it is part of a normal response and not an indication of dysfunctional adjustment in most cases.

Overall, the majority of women and their partners seem to adjust well to the considerable stress of several unsuccessful treatment cycles, suggesting that standard psychological interventions in the patient population do not

seem to be indicated. However, attention has to be paid to early identification of women at risk of developing emotional problems as the result of unsuccessful treatment, who might benefit from psychological intervention. The focus of these interventions should be adjustment to possible childlessness and acceptance of the fertility problems, since the possible childlessness and infertility seems the most important stressor in IVF and ICSI treatment.



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## **Samenvatting**

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## SAMENVATTING

In vitro fertilisatie (IVF) of intracytoplasmische sperma injectie (ICSI) zijn behandelingen voor paren met vruchtbaarheidsproblemen. IVF of ICSI zijn meestal de laatste behandelingsmogelijkheden voor deze mensen. Een behandeling kan meerdere cycli omvatten. Een cyclus bestaat uit het stimuleren van eicelrijping, als er genoeg eicellen zijn gerijpt vindt er een eicel punctie plaats. Bij IVF worden de eicellen in een petrischaal samengebracht met de zaadcellen. Bij ICSI wordt een zaadcel met behulp van een micropipet direct in het cytoplasma van de eicel gebracht. Wanneer er na twee dagen sprake is van een bevruchting worden er maximaal twee embryo's teruggeplaatst in de baarmoeder. Twee weken na de terugplaatsing kunnen vrouwen een zwangerschapstest uitvoeren. Wanneer er geen zwangerschap is opgetreden kan het paar na ongeveer een maand een volgende cyclus starten. Ten tijden van het onderzoek vergoedde de meeste Nederlandse zorgverzekeraars drie behandelingscycli. Eventuele volgende cycli moest het paar zelf bekostigen.

Het doel van dit proefschrift was om inzicht te krijgen in de emotionele reactie van vrouwen op een of meer niet succesvolle behandelingscycli vanaf het moment voorafgaand aan de eerste behandelingscyclus tot 6 maanden na de laatste cyclus. Ook werd nagegaan welke factoren deze emotionele reactie beïnvloedden.

Het eerste deel van dit proefschrift behandelt de emotionele reactie op de eerste behandelingscyclus: korte termijn beloop. In het tweede deel komt aan bod welke factoren dit korte termijn beloop beïnvloeden. In het derde deel ten slotte, staat het lange termijn beloop centraal samen met de factoren die dit beloop beïnvloeden.

### **Deel 1. Korte termijn beloop van angst, depressie en tevredenheid met partner en seksuele relatie.**

In *hoofdstuk 2* beschrijven we in welke mate vrouwen voor de start van een eerste IVF of ICSI behandelingscyclus, voor wat betreft hun emotionele status afwijken van andere vrouwen van hun leeftijd. De literatuur op dat gebied laat een tegenstrijdig beeld zien. Er zijn studies die meer negatieve emotie rapporteren bij vrouwen voor de start van de behandeling. Andere studies vinden echter geen verschillen met normgroepen. De vrouwen in



onze onderzoeksgroep weken wat hun niveau van angst en depressie betreft niet af van Nederlandse normgroepen. De verschillende resultaten tussen de studies kunnen gedeeltelijk verklaard worden door verschillen in meetmomenten. Sommige studies maken geen onderscheid naar het aantal eerdere behandelingscycli en beschrijven de emotionele status van vrouwen die soms al een of meer mislukte behandelingscycli achter de rug hebben. Dat verklaart mogelijk waarom het angst en depressie niveau van deze vrouwen hoger is dan dat van normgroepen. In de huidige studie werd uitgegaan van de emotionele status voor de start van de eerste behandelingscyclus. Op dat moment vertonen vrouwen niet meer of minder angst of depressie dan andere vrouwen van hun leeftijd.

In *hoofdstuk 2* en *hoofdstuk 3* wordt vervolgens ingegaan op de emotionele reactie op een niet succesvolle eerste behandelingscyclus: de korte termijn reactie. De resultaten laten een stijging in angst en depressie zien. Zwangere vrouwen, echter, lieten een daling zien van angst en depressie. Dit is een bevestiging van resultaten uit eerdere studies. Voor de start van de behandeling vertoonden 11 procent van de vrouwen sub klinisch relevante vormen van depressie, na afloop van de eerste niet succesvolle behandelingscyclus, steeg dat percentage naar 21.

Een ander opvallend resultaat was dat, al voor de start van de behandeling, vrouwen die niet zwanger werden een hoger niveau van depressie lieten zien dan vrouwen die wel zwanger werden. Dit suggereert een mogelijke relatie tussen depressie en de slaagkans van de behandeling die we in een andere studie, waarover elders, niet in dit proefschrift, is gerapporteerd, inderdaad bevestigd hebben. (J.M.J. Smeenk, C.M. Verhaak, A. Eugster, A. van Minnen, G.A. Zielhuis, D.D.M. Braat. (2001). The effect of anxiety and depression on the outcome of in vitro fertilisation. *Human Reproduction* 16, 1420-1423.).

Hoofdstuk drie beschrijft naast angst en depressie als emotionele reactie op de vruchtbaarheidsbehandelingen ook het beloop van de tevredenheid met de partner- en seksuele relatie beschreven. Ook hier bleken vrouwen voorafgaand aan de eerste behandelingscyclus niet af te wijken van normgroepen. Ze vertoonden niet meer of minder onvrede met hun partner- en seksuele relatie dan andere vrouwen van hun leeftijd. Na afloop van de eerste behandelingscyclus veranderde de tevredenheid met de partnerrelatie niet, dit was onafhankelijk van het resultaat van de cyclus. De onvrede met de seksuele relatie steeg echter wel: zowel na een succesvolle als na een niet succesvolle cyclus. Exploratieve analyses lieten

zien dat de stijging in onvrede bij zwangere vrouwen mogelijk te maken heeft met een verminderde behoefte aan geslachtsgemeenschap tijdens de zwangerschap. Bij niet zwangere vrouwen kan het samenhangen met de verhoogde depressieve stemming als gevolg van het niet slagen van de behandeling. In het derde hoofdstuk gingen we ook in op de vraag welke plannen vrouwen voorafgaand aan de eerste behandelingscyclus hebben voor eventuele volgende behandelingscycli wanneer er geen spraken is van zwangerschap. Tweeëntachtig procent van de vrouwen gaf aan in dat geval een nieuwe cyclus te willen starten. Vervolgens werd nagegaan wat het daadwerkelijke gedrag van deze vrouwen was. Slechts 65 procent van de niet zwangere vrouwen bleek na de eerste mislukte cyclus inderdaad een tweede cyclus te starten. Vrouwen die niet doorgingen met de behandeling lieten voorafgaand aan de eerste cyclus al hogere niveaus van angst en depressie zien dan vrouwen bij wie dat niet het geval was.

## **Deel 2. Factoren die bijdragen aan het korte termijn beloop van angst en depressie.**

Deel twee van het proefschrift beschrijft onderzoek naar factoren die bijdragen aan het korte termijn beloop van angst en depressie na een eerste niet succesvolle behandelingscyclus. Op basis van stress kwetsbaarheidmodellen werd een brede set factoren geselecteerd die van belang kunnen zijn. In *hoofdstuk 4* komen twee factoren aan de orde die mogelijk bijdragen aan het korte termijn beloop van angst: neuroticisme en selectieve aandacht. Neuroticisme, of negatieve affectiviteit, gedefinieerd als de neiging in relatief sterke mate te reageren op dreigende informatie, werd beschouwd als een algemene, risico factor voor het ontwikkelen van zowel angst als depressie. Cognitieve theorieën over informatieverwerking gaan er van uit dat niet bewuste selectieve aandacht voor dreigende informatie ook een belangrijke kwetsbaarheidfactor is voor de ontwikkeling van angst. In hoofdstuk vier wordt duidelijk dat deze niet bewuste selectieve aandacht inderdaad een bijdrage leverde aan het korte termijn beloop van angst bij vrouwen na een niet succesvolle behandeling, ook na statistische controle voor neuroticisme. Dit komt overeen met de schaarse empirische studies op dit terrein die laten zien dat niet bewuste selectieve aandacht ten aanzien van dreigende informatie verandering in angst voorspelden in niet klinische populaties. De resultaten laten zien dat kwetsbaarheid voor het ontwikkelen van angst zowel op automatisch (niet

bewust) als op strategisch (bewust) niveau tot uitdrukking komt. Zowel neuroticisme als niet bewuste selectieve aandacht voor dreigende informatie beïnvloeden dus beide het beloop van angst als gevolg van een niet succesvolle behandelingscyclus beïnvloeden.

*Hoofdstuk 5* beperkt zich tot kwetsbaarheidfactoren op strategisch niveau. Centraal staat de vraag welke strategische factoren het beloop van angst en depressie na een eerste niet succesvolle behandelingscyclus beïnvloeden. Uitgaande van algemene stress kwetsbaarheidmodellen uit de psychologie werden vier groepen factoren onderscheiden die verondersteld werden hierbij een rol te spelen: persoonlijkheidskenmerken (neuroticisme, extraversie, optimisme), betekenis van vruchtbaarheidsproblemen (hulpeloosheid, acceptatie), coping strategieën (actief probleem oplossen en vermijding), algemene aspecten van sociale steun (waargenomen steun), en sociale steun in de context van de partnerrelatie (algemene tevredenheid met de partnerrelatie, tevredenheid met de seksuele relatie). Uit de resultaten bleek dat een hoger niveau van neuroticisme, meer hulpeloosheid, minder acceptatie en meer onvrede met de partnerrelatie bijdroegen aan de stijging in angst en depressie na een eerste niet succesvolle behandelingscyclus. Weinig algemene sociale steun droeg alleen bij aan een stijging in angst. Ook na statistische controle voor neuroticisme bleken genoemde factoren bij te dragen aan het beloop van de emotionele reactie op de eerste behandelingscyclus.

Het belang van neuroticisme als kwetsbaarheidsfactor is bekend en wordt ook in dit proefschrift bevestigd voor wat betreft de emotionele reactie op een niet succesvolle vruchtbaarheidsbehandeling. Met betrekking tot de rol van 'betekenis van de vruchtbaarheidsproblemen' als kwetsbaarheidsfactor werd verondersteld dat hulpeloosheid met name een bijdrage zou leveren aan het korte termijn beloop van depressie, hulpeloosheid droeg echter ook bij aan het beloop van angst. Wel was de bijdrage aan depressie prominenter. Dit ondersteunt de centrale rol van hulpeloosheid in het ontstaan van depressie die ook in andere populaties is aangetoond. Acceptatie droeg zowel bij aan het beloop van angst als aan het beloop van depressie. Dit komt overeen met eerdere studies die lieten zien dat acceptatie een beschermende factor was in het ontwikkelen van een negatieve emotionele reactie op een niet succesvolle eerste behandelingscyclus en is in lijn met studies die de gunstige rol van acceptatie beschrijven als reactie op oncontroleerbare chronische stressoren. Dit suggereert dat mensen die het bestaan van de chronische

stressor erkennen en tevens in staat zijn met de consequenties ervan te leven minder negatieve emotie ervaren als gevolg van die stressor.

Coping factoren leverden geen bijdrage aan het korte termijn beloop van noch angst, noch depressie. Dit kan mogelijk verklaard worden uit de lange tijdsperiode tussen het meten van coping (voor de start van de eerste cyclus) en de emotionele reactie (4 weken na de eerste cyclus, ongeveer 2 tot 3 maanden na de eerste meting). In deze periode heeft de behandeling plaats gevonden. Deze behandeling bestaat uit verschillende aspecten die mogelijk vragen om verschillende coping stijlen: de dreiging van de behandeling, de onzekerheid met betrekking tot de uitkomst van de behandeling, het verlies van de hoop op zwangerschap. Wellicht zijn de coping maten die in deze studie zijn gebruikt, te algemeen geweest om het mogelijk verschil in coping effectiviteit bij verschillende aspecten van de behandeling goed te kunnen meten.

De veronderstelde rol van sociale steun als beschermende factor voor de emotionele reactie op een niet succesvolle behandelingscyclus werd in deze studie ondersteund. Minder tevredenheid met de partnerrelatie en minder waargenomen sociale steun bleken bij te dragen tot meer angst en depressie na de eerste niet succesvolle behandelingscyclus.

### **Deel 3. Het lange termijn beloop van angst, depressie en tevredenheid met de partner- en seksuele relatie en factoren die dat beloop beïnvloeden.**

In *hoofdstuk 6* wordt het lange termijn beloop van angst en depressie beschreven. De resultaten lieten een stijging van angst en depressie zien tussen de start van de eerste behandelingscyclus en net na de laatste cyclus. In de zes maanden na de laatste cyclus werd geen verandering gezien. Dit betekent dat er geen tekenen van herstel waren in de zes maanden na de laatste behandeling. Zwangere vrouwen echter, lieten in deze zes maanden wel een daling in angst en depressie zien.

Het is opmerkelijk dat in de zes maanden na de laatste niet succesvolle cyclus geen daling in angst en depressie werd gesignaleerd. De verwachting was dat angst zou dalen omdat de angst voor de behandeling en de onzekerheid omtrent de uitkomst van de behandeling niet meer actueel zijn. Wellicht wordt het uitblijven van een daling in angst verklaard door het feit dat paren ook na wat een laatste behandelingscyclus zou zijn, doorgaan met overwegingen over mogelijke verdere behandelingen. Uit

eerdere studies is gebleken dat paren lang na het afsluiten van hun vruchtbaarheidsbehandelingen nog steeds twijfelen over mogelijk verder te nemen behandelingsinitiatieven. Ook geven veel van hen aan een nieuwe therapie te starten wanneer die zich zou aandienen. Het is dus mogelijk dat vrouwen zes maanden na de laatste behandeling niet het idee hebben dat ze de vruchtbaarheidsbehandelingen hebben afgesloten; de uitkomst is dan niet definitief, de onzekerheid blijft bestaan.

Net als het uitblijven van een daling van het angst niveau, bleef ook de verwachte lichte daling depressie achterwege. Eerdere studies naar het beloop van de emotionele reactie na verliezen zoals een miskraam of perinatale sterfte, laten een daling van depressie zien in het eerste half jaar na het verlies. Het is mogelijk dat de verwerking van het niet slagen van vruchtbaarheidsbehandelingen, en daarmee ook de min of meer definitieve onvruchtbaarheid, complexer is dan de verlieservaringen die in deze studies zijn onderzocht. Verwerking van ongewilde kinderloosheid betekent het verlies van een droom, van een ideaal, en niet van iets tastbaars dat deel was van het dagelijks leven.

Onze resultaten laten zien dat het merendeel van de vrouwen zich na een half jaar goed heeft aangepast aan het niet slagen van de behandelingen. Een aanzienlijke groep echter, laat sub klinische vormen van angst en/of depressie zien. Eerder vonden wij dat voor de eerste behandelingscyclus ongeveer elf procent van de vrouwen boven de grens van sub klinisch relevante symptomen van angst of depressie scoort (hoofdstuk 2 en 3), net na de laatste cyclus is dat vierentwintig procent voor angst en twintig voor depressie. Zes maanden na de laatste behandeling liet twintig procent van de vrouwen nog sub klinische vormen van angst zien naast vijftwintig procent van depressie. Deze vrouwen vormen een risicogroep voor het ontwikkelen van ernstigere vormen van angst en depressie in de nabije toekomst.

In *hoofdstuk 6* werd verder nagegaan welke factoren het lange termijn beloop van angst en depressie beïnvloeden. Dezelfde set van strategische factoren die gebruikt was bij het onderzoek naar de bijdrage aan het korte termijn beloop werden onderzocht voor het lange termijn beloop. De resultaten lieten zien dat een hoger niveau van neuroticisme en meer onvrede met de partnerrelatie bijdroegen aan een stijging in angst en depressie. Minder optimisme, minder acceptatie en meer hulpeloosheid droegen bij tot een stijging in depressie, terwijl minder waargenomen sociale steun bijdroeg tot een stijging in angst. De resultaten onderstrepen

de centrale rol van neuroticisme of negatieve affectiviteit in de ontwikkeling van zowel angst als depressie. Daarnaast werd ondersteuning gevonden voor de invloed van hulpeloosheid en acceptatie ten aanzien van vruchtbaarheidsproblemen in het ontwikkelen van depressie en verschillende aspecten van sociale steun in de ontwikkeling van zowel angst als depressie.

De resultaten lieten zien dat factoren die van invloed zijn op het korte termijn beloop van de emotionele reactie op niet succesvolle IVF of ICSI, grotendeels overeenkomen met de factoren die het lange termijn beloop beïnvloeden. Dit biedt de mogelijkheid voorafgaand aan de eerste behandelingscyclus die vrouwen te selecteren die groter risico lopen op het ontwikkelen van ernstige emotionele problematiek bij het niet slagen van de behandeling. Op basis van deze risico factoren kan een screeningsinstrument worden ontwikkeld dat deze vrouwen al in een vroeg stadium kan identificeren. Aan hen kan dan gerichte psychosociale ondersteuning worden geboden. Op de eerste plaats binnen de reguliere zorg, maar indien noodzakelijk ook door een psycholoog.

Om inzicht te krijgen in het effect van de IVF of ICSI behandeling op de partner- en seksuele relatie werd in *hoofdstuk 7* het lange termijn beloop van tevredenheid met partner- en seksuele relatie onderzocht. Uit de resultaten bleek dat de tevredenheid met de partnerrelatie eigenlijk niet veranderde gedurende een of meer niet succesvolle behandelingscycli. Er was echter een substantiële stijging in onvrede met de seksuele relatie zowel na een succesvolle, als na een niet succesvolle behandeling. De stijging in onvrede bij zwangere vrouwen wordt mogelijk verklaard door verminderde behoefte aan geslachtsgemeenschap die wel vaker gesignaleerd wordt bij zwangere vrouwen, zeker na vruchtbaarheidsbehandelingen. Stijging in onvrede met de seksuele relatie na een niet succesvolle behandeling zou verband kunnen hebben met een algemeen verminderd plezier in seks. Dit kan te maken hebben met de druk van de behandeling, maar ook met het zoeken naar een nieuwe invulling van seks onafhankelijk van de voortplanting. In het algemeen lijkt het van belang paren voor te bereiden op het mogelijk negatieve effect van de behandeling op de seksuele relatie.

### **De emotionele reactie van mannen**

In dit proefschrift stond de emotionele reactie van vrouwen op een niet succesvolle behandeling centraal. Daarnaast verkenden we echter ook de emotionele reactie van hun partners (allemaal mannen). Eerdere studies rapporteerden minder emotionele reactie op vruchtbaarheidsproblemen bij mannen dan bij vrouwen, terwijl zowel vrouwen als mannen vruchtbaarheidsproblemen als een grote belasting ervaren. De mannen die participeerden in de huidige studie vertoonden nauwelijks verandering in emotionele status tijdens de diverse behandelingscycli. Dit ondersteunt resultaten uit eerdere studies over de emotionele reactie van mannen op vruchtbaarheidsproblemen. Ofschoon de belasting die de behandeling oproept bij zowel vrouwen als mannen groot lijkt te zijn, uit zich dat bij mannen niet in een negatiever emotioneel welbevinden. Verder onderzoek is nodig om meer inzicht te krijgen in het mogelijke verschil in betekenis van vruchtbaarheidsproblemen tussen vrouwen en mannen.

### **De emotionele reactie op succesvolle behandeling**

Een succesvolle IVF of ICSI behandeling leidt tot vermindering van spanning en depressieve stemming. Net na de succesvolle cyclus zijn niveaus van angst en depressie al lager dan voorafgaand aan de behandeling. De stress van de behandeling speelt kennelijk geen rol meer. Wij veronderstellen dat de negatieve emotionele reactie van vrouwen na een niet succesvolle behandeling toegeschreven moet worden aan het niet slagen van de behandeling. Het lijkt dus niet de vruchtbaarheidsbehandeling zelf te zijn die de emotionele reactie oproept, maar de dreiging van de kinderloosheid en het verlies van hoop op zwanerschap.

### **Beperkingen van de studie**

Een belangrijke beperking van de studie is het relatief hoge aantal vrouwen dat voortijdig met het onderzoek stopte. Deze uitval was met name hoog bij vrouwen na een niet succesvolle behandeling. Dat betekent dat zwangere vrouwen oververtegenwoordigd zijn in deze studie. Vrouwen die voortijdig stopten met het onderzoek waren niet meer of minder angstig of depressief dan vrouwen die deel bleven nemen. Ook verschilden zij wat betreft hun tevredenheid met partner- en seksuele relatie niet van de andere vrouwen. Wel bleken vrouwen die voortijdig stopten met het onderzoek vaker niet

zwanger te zijn dan vrouwen die wel bleven deelnemen. Deze vrouwen vertoonden voor de eerste behandelingscyclus al meer stress dan vrouwen die de behandeling wel voortzetten. Deze selectieve uitval betekent dat de resultaten van deze studie niet zonder meer gegeneraliseerd kunnen worden naar vrouwen die de behandeling vroegtijdig gestaakt hebben. Door de uitval uit het onderzoek was de power van de studie te beperkt om een totaal model van kwetsbaarheidfactoren te toetsen voor de emotionele reactie op zowel de korte als de lange termijn.

Een andere beperking van de studie is de definiëring van de laatste behandelingscyclus. Het is mogelijk dat een groep van niet zwangere vrouwen in onze follow-up studie nog steeds verdere of andere behandelingsmogelijkheden overwegen. Het probleem van het onderzoeken van de emotionele reactie op de laatste vruchtbaarheidsbehandeling is dat het bijna onmogelijk is van 'laatste' te spreken zeker nu behandelingsmogelijkheden, ook voor oudere vrouwen, nog steeds worden uitgebreid. Dit kan beslissingen van vrouwen om definitief te stoppen met vruchtbaarheidsbehandelingen bemoeilijken. Het rouwproces omtrent het omgaan met de definitieve kinderloosheid kan echter pas beginnen als er geen overwegingen voor verdere behandelingen meer zijn. Het is mogelijk dat het niveau van depressie bij vrouwen in deze studie zelfs hoger zou zijn als alleen vrouwen bij het onderzoek waren be trokken die definitief andere vruchtbaarheidsbehandelingen achter zich hebben gelaten.

### **Suggesties voor verder onderzoek**

Uit dit proefschrift blijkt dat zes maanden na de laatste behandelingscyclus een aanzienlijk deel van de vrouwen sub klinische relevante symptomen van angst en/ of depressie laat zien. Longitudinale studies die vrouwen volgen tot enkele jaren na de laatste vruchtbaarheidsbehandeling moeten inzicht geven in het verdere verloop van de emotionele reactie. Het is van belang te weten of angst en depressie niveaus twee jaar na de laatste cyclus weer gedaald zijn tot het uitgangsniveau, iets wat in studies naar de reactie op andere ernstige verlieservaringen wel wordt gerapporteerd. Of moet het uitblijven van een herstel in emotionele status in de zes maanden na de laatste cyclus gezien worden als een teken van een gecompliceerd rouwproces dat veroorzaakt wordt door de specifieke kenmerken van het probleem van de dreigende onvruchtbaarheid. Mocht dat laatste het geval



zijn dan heeft dat implicaties voor de klinische praktijk, omdat deze vrouwen mogelijk baat hebben bij aanvullende psychologische zorg.

Een ander interessant punt voor verder onderzoek is de rol van mogelijk positieve ervaringen die paren kunnen opdoen tijdens de IVF en ICSI behandeling en de begeleidende positieve emoties. De positieve emotionele reacties op ernstige levensgebeurtenissen blijken in een algemene populatie relatief onafhankelijk op te treden van negatieve reacties. Deze positieve reactie zou naast de negatieve, die in dit proefschrift zijn onderzocht, te maken kunnen hebben met het ontwikkelen van andere levensdoelen dan het krijgen van kinderen. De relatie tussen acceptatie en deze positieve emotionele reactie zou in dit kader interessant kunnen zijn.

Verder onderzoek is ook gewenst naar het beloop van de tevredenheid met partner- en/ of seksuele relatie beïnvloeden, omdat de sociale steun die de partnerrelatie kan bieden een belangrijke buffer kan zijn voor het optreden van een negatieve emotionele reactie als gevolg van het niet slagen van de behandeling. Hier kan dan in eventuele psychologische interventies op worden aangesloten.

Deze studie heeft informatie opgeleverd over factoren die een rol spelen in de kwetsbaarheid van vrouwen voor het ontwikkelen van relatief meer angst en depressie als gevolg van niet succesvolle IVF of ICSI. Op basis hiervan kan een korte vragenlijst worden ontwikkeld. Inmiddels wordt in het UMC ST. Radboud onderzoek uitgevoerd naar de voorspellende waarde van deze korte lijst voor de emotionele reactie op het niet slagen van een eerste behandelingscyclus. Gebaseerd op een dergelijke korte vragenlijst kunnen vervolgens voor risico groepen van vrouwen psychologische interventies worden ontwikkeld, geëvalueerd en bij gebleken effectiviteit worden geïmplementeerd in de dagelijkse klinische praktijk.

### **Implicaties voor de klinische praktijk**

De meeste paren blijken de stress die de niet succesvolle IVF- of ICSI behandeling met zich mee brengt goed zelf kunnen oplossen. Ongeveer een vijfde tot een kwart van de vrouwen echter, vertoont zes maanden na het afsluiten van de behandeling nog steeds sub klinisch relevante symptomen van angst en/of depressie. Deze vrouwen vormen een risicogroep voor het ontwikkelen van psychopathologie in de nabije toekomst en zouden baat kunnen hebben bij psychologische interventie.

De vruchtbaarheidsbehandeling zelf lijkt niet de belangrijkste bron van emotionele belasting. Het resultaat van de behandeling blijkt belangrijker. De dreigende onvruchtbaarheid en het verlies van hoop op een zwangerschap lijken de belangrijkste negatieve emotionele reacties op te roepen. Dit proefschrift laat zien dat neuroticisme een belangrijke bijdrage levert aan het beloop van de emotionele reactie op een niet succesvolle behandeling. Neuroticisme is een aangeboren, relatief stabiel kenmerk dat niet erg gevoelig is voor verandering. Het huidige proefschrift laat echter zien dat betekenis van de vruchtbaarheidsproblemen en sociale steun ook een belangrijke bijdrage leveren aan de emotionele reactie op de niet succesvolle behandeling. Dat betekent dat de evaluatie van een leven zonder kinderen, de consequenties van kinderloosheid voor de partnerrelatie en relatie met familie en vrienden belangrijke aandachtspunten kunnen zijn in psychologische interventies.

Gynaecologen, IVF-artsen en verpleegkundigen kunnen het proces van acceptatie van vruchtbaarheidsproblemen en de communicatie tussen partners stimuleren door deze punten te bespreken met hun patiënten. Ze kunnen vragen naar mogelijke plannen die het paar heeft indien de behandelingen geen succes hebben, ze kunnen ingaan op mogelijke motivatieverschillen binnen het paar ten aanzien van verdere behandelingsmogelijkheden. Ook kunnen klinici een belangrijke rol spelen in de voorlichting van paren op emotionele reacties die ze kunnen verwachten. Verhoogde spanning en een depressieve stemming zijn natuurlijke reacties op een niet succesvolle behandeling. Deze voorbereidende informatie in de vorm van psychoeducatie kan bij paren het gevoel van controle vergroten over hun eigen emotionele reactie op de uitkomst van de behandeling. Het kan ze het vertrouwen geven dat in de meeste gevallen deze emoties onderdeel zijn van een normale reactie op zo'n ingrijpende gebeurtenis en dat ze geen indicatie zijn van psychopathologie.

In het algemeen lijkt een meerderheid van de vrouwen en mannen uiteindelijk goed om te kunnen gaan met het eventuele niet slagen van de behandeling. Dit betekent dat standaard psychologische interventies voor alle IVF- of ICSI paren niet geïndiceerd zijn. Het is echter van belang dat paren die risico lopen op het ontwikkelen van ernstige emotionele problemen als gevolg van het niet slagen van de behandeling in een vroeg stadium worden geïdentificeerd. Deze paren zouden dan baat kunnen hebben bij aanvullende psychologische interventies. De nadruk van die

interventies zal moeten liggen op betekenis van kinderloosheid, het stimuleren van acceptatie van de mogelijk definitieve onvruchtbaarheid en de invloed van vruchtbaarheidsproblemen op de partnerrelatie en op andere sociale contacten.

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door die gigantische dataverzameling heen had moeten ploeteren. Dank voor je humor en je onuitputtelijke inzet.

Ook de andere leden van de begeleidingscommissie van het 'Stress en IVF' onderzoek (Drs. A. Eugster, Prof. Dr. C.A.L. Hoogduin, Prof. Dr. J.M.W.M. Merkus, Prof. Dr. A.J.J.M. Vingerhoets, en Prof. Dr. G.A. Zielhuis) hebben mij met hun kritisch commentaar en hun goede suggesties steeds gestimuleerd het onderzoek vanuit verschillende perspectieven te benaderen. De multidisciplinaire samenwerking kreeg in deze commissie op vruchtbare wijze gestalte.

Ook de artsen, verpleegkundigen, mensen van het lab, secretaresses en andere medewerkers van de afdeling Fertendo hebben een onmisbare bijdrage geleverd aan het onderzoek. Jullie gastvrijheid, belangstelling en collegialiteit hebben het onderzoek mogelijk gemaakt en hebben voor een prettige samenwerking gezorgd. Jullie humor heeft veel dataverzamelings-stress gerelativeerd. De IVF-artsen (Ilse Feenstra, Esther Haagen, Bea Lintsen, Marieke Lukassen en Gwendoline Wolderingh) en -verpleegkundigen (Leny Blonk, Thea ten Haaf, Karin van Mook, Yvon Rijken, Rian Stiphout, Josee Terken en Ellen van de Vorst) wil ik graag in bedanken voor hun steun aan het onderzoek.

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De Studiegroep Onderzoek Reproductieve Technieken (SORT) onder voorzitterschap van Frank van Balen heeft mij vanaf het begin de gelegenheid gegeven mijn onderzoek voor breder publiek te presenteren. Ik ben hen daar zeer erkentelijk voor.

The special interest group 'Psychology and Counselling' of the European Society of Human Reproduction and Embryology (ESHRE), with its unequalled chairman Jacky Boivin provided the opportunity to share results of international studies and implementations of psychosocial care in different countries. Jacky, special thanks for your never failing enthusiasm

for the issue of psychology and infertility. The annual ESHRE conferences in those beautiful places in Europe were intellectually challenging, and very enjoyable.

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Lieve Hub, nu ben ik dan aan de beurt. De inspiratie die wij elkaar geven valt niet in woorden te beschrijven. Ik hoop er nog lang van te kunnen genieten.

# Curriculum vitae

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## Curriculum vitae

Christianne Verhaak werd geboren op 19 december 1959 in Heesch bij Oss. Zij haalde haar VWO diploma aan het Elshofcollege in Nijmegen. Korte tijd studeerde zij sociale geografie in Nijmegen waarna zij in 1980 startte met de studie psychologie. In 1987 studeerde zij af aan de Katholieke Universiteit Nijmegen in de cultuur- en godsdienst psychologie (Prof. Dr. V. Welten). Zij werkte van 1987 tot 1988 bij de Stichting Emancipatie Flevoland in Lelystad waar zij een onderzoek uitvoerde naar de positie van vrouwen in de provincie Flevoland. Daarnaast werkte zij van 1987 tot 1995 als onderzoeker bij het Instituut voor Toegepaste Sociale Wetenschappen in Nijmegen bij de afdeling Onderwijs Achterstanden (Dr. P. Jungbluth en Dr. P.Tesser), met als aandachtsgebied de sociaal emotionele positie van kansarme Nederlandse en allochtone kinderen in het onderwijs.

In 1995 kwam zij als psycholoog / onderzoeker in dienst bij de afdeling Medische Psychologie van het Universitair Medische Centrum St. Radboud in Nijmegen waar zij bij de afdeling Radiotherapie onderzoek uitvoerde naar de communicatie tussen arts en patiënt (Prof. Dr. F.W. Kraaimaat, Prof. Dr. W.A.J. van Daal en Drs. A. Staps). Van 1998 tot 2002 werkte zij als onderzoeker aan het project 'Stress en IVF', (Prof. Dr. F.W. Kraaimaat, Prof. Dr. D.D.M. Braat, Dr. J.A.M. Kremer en Dr. A. van Minnen) gesubsidieerd door het Praeventiefonds/ ZonMw, hetgeen geresulteerd heeft in dit proefschrift. In 2002 behaalde zij haar registratie tot gezondheidszorgpsycholoog. Sinds die tijd is zij werkzaam als psycholoog bij de sectie kinderpsychologie van het UMC St. Radboud en is zij actief in de patiëntenzorg bij de afdelingen Algemene Pediatrie, Kinder Intensive Care en het Hemofilie Behandelcentrum. Daarnaast participeert zij in onderzoek bij het Schisisteam, en de afdelingen Klinische Genetica, Obstetrie en Gynaecologie. Tevens geeft zij onderwijs aan studenten geneeskunde. Recentelijk is zij toegetreden tot de commissie Ethiek van het UMC St. Radboud.

Christianne Verhaak is sinds 1988 getrouwd met Hub Zwart. Samen kregen zij twee dochters: Lidewij (1992) en Hadewijch (1993).



