The Psychological Impact of IVF Treatment

Cora de Klerk

The work presented in this thesis was performed at the Department of Medical Psychology and Psychotherapy, Erasmus MC, Rotterdam, in close collaboration with the Division of Reproductive Medicine, Erasmus MC, Rotterdam, and the Department of Reproductive Medicine, University Medical Center, Utrecht.

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The Psychological Impact of IVF Treatment

De psychologische impact van IVF-behandeling

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Ter herinnering aan Henrik

Kijk
Ik kleed me
voor je uit. Kom dichterbij
en leg je hand op mijn buik
Voel je de dromen die hier wonen?
Vlij je hoofd tegen
mijn buik
Luister

Judith Uyterlinde ‘Eisprong’

Contents

Chapter 1

General introduction

Introduction

And when Rachel saw that she bore Jacob no children, Rachel envied her sister; and she said unto Jacob: 'Give me children, or else I die.' And Jacob's anger was kindled against Rachel; and he said: 'Am I in God's stead, who hath withheld from thee the fruit of the womb?' And she said: 'Behold my maid Bilhah, go in unto her; that she may bear upon my knees, and I also may be builded up through her. And she gave him Bilhah her handmaid to wife; and Jacob went in unto her. And Bilhah conceived, and bore Jacob a son. And Rachel said: 'God hath judged me, and hath also heard my voice, and hath given me a son.' (Genesis 30:1-6)

The biblical tale about Rachel and Jacob, over 3500 years old, illustrates that involuntary childlessness can cause a broad range of emotions in couples. Furthermore, it shows us that partners may cope with their infertility in different ways and have different beliefs about the cause of their childlessness. The most important message of this story however, is that couples are willing to go to great lengths to fulfil their wish for a child of their own.

In the last 30 years, several Assisted Reproductive Technologies (ART) have been introduced, including In Vitro Fertilization (IVF) and Intracytoplasmic Sperm Injection (ICSI), which enable sub-fertile couples to have a child that is genetically theirs. The first baby to be conceived from IVF treatment, Louise Brown, was born in 1978. Since then, over a million babies have been born around the world with the help of ART [1]. Between 1996 and 2000, one out of every 61 children born in the Netherlands was conceived through IVF or ICSI [2].

IVF is a time-consuming and intrusive treatment. Current treatment protocols require the woman to begin injections with a gonadotropin-releasing hormone (GnRH) agonist to prevent premature ovulation in the mid-luteal phase of her pretreatment menstrual cycle. Two weeks later she must commence additional daily injections of follicle stimulating hormone (FSH) to stimulate the growth of multiple follicles. The aim is to produce multiple oocytes for fertilization in vitro. Frequent blood tests and ultrasound scans are performed to monitor the development of ovarian follicles. When enough follicles have sufficiently matured, the oocytes are aspirated from the ovaries under transvaginal ultrasound control. On the same day, sperm is produced by the father or sperm donor. The oocytes are then fertilised with the sperm outside the mother's body. Two to five days later, one or more of the resulting embryos are transferred to the mother's uterus. During the next twelve to fourteen days, the couple must wait until they can take a pregnancy test to determine whether treatment was successful, while the woman continues medication to support successful implantation of the embryos. The chance that a pregnancy will occur is approximately 1 in 5.

Medical risks of IVF treatment

Standard IVF treatment, as briefly described above, is not without health risks. Ovarian suppression with the use of GnRH agonists can lead to menopausal symptoms, such as hot flushes, vaginal dryness, headaches and mood swings [3-5]. Furthermore, a small percentage (0.1-0.5%) of women receiving ovarian stimulation will develop ovarian hyperstimulation syndrome which can result in serious and even life-threatening medical complications [6]. The long-term maternal risks associated with ovarian stimulation remain unclear due to a lack of reliable studies [7]. The most important complication of IVF however, is multiple pregnancy, which is associated with a variety of maternal, foetal en neonatal complications. In 2003, about twenty-five percent of IVF deliveries in Europe were multiples [8].

One of the major maternal complications of multiple pregnancy is hypertension. Severe hypertension occurs 2-3 times more often in twin than in singleton pregnancies [9]. Pre-eclampsia, or pregnancy toxemia, is about three times more common in twin than in singleton pregnancies [10]. Multiple pregnancies not only lead to an increased likelihood of medical problems in the carrying mothers, but also in the offspring themselves. Compared with singletons, twins are at approximately 5-fold increased risk of foetal death. Additionally, neonatal death occurs 7 times more often in twins [11]. The major causes of perinatal mortality and morbidity in multiple pregnancies are preterm delivery and low birth weight. As a result of these problems, women carrying multiples are at increased risk of requiring treatment and extended hospitalisation.

Women's experiences of IVF treatment

Despite the relatively low chance of achieving a pregnancy in one IVF cycle, many women embarking on treatment have unrealistic expectations about treatment success [12]. This is what Kalbian [13] calls 'The hope narrative': the infertile woman strongly believes that the fertility physicians are able to help her achieve a successful pregnancy. In order to achieve this goal, the woman feels she has to completely surrender her body to her physician. Indeed, many women report a lack of control during the process of infertility treatment [14]. They feel they have little choice but to succumb to the invasive investigations and procedures the doctors prescribe. A very private aspect of their lives, namely reproduction, becomes medicalised. As a result of this process, feelings of depersonalisation can emerge. Women may feel they are not a person anymore, but feel as if they are being reduced to body parts instead. Even after successful treatment, women retrospectively describe infertility treatment as being physically and emotionally painful, while some women even reported feeling 'hurt' or 'damaged' [14].

Undergoing infertility treatment also has an impact on the woman's social and professional life [12]. Social activities are often put on hold during a treatment cycle, as many women are not able or willing to share their experiences with others. Furthermore, the frequent hospital visits may result in absence from work. The demands of treatment also put pressure on the partner relationship. Partners often cope differently with treatment related strain and this may lead to disagreement about whether to continue treatment or not. Many couples find it difficult to make the final decision about ending IVF treatment [12]. Being diagnosed with infertility may evoke strong feelings of deficiency in a woman, who feels that motherhood is the norm. She may feel social pressure to reproduce from her family, friends or even society. According to Franklin [15], the paradoxical nature of IVF treatment itself makes it more difficult for women to come to terms with their infertility. There are always newer assisted reproductive technologies to try which makes the decision to end treatment a difficult one. As Franklin [15] puts it, 'IVF is a choice, but not a choice. It is a resolution, but not a resolution'.

Psychological models of infertility

In lay aetiology, psychological problems are often believed to have a negative effect on fertility. The origin of this belief can be dated back to the 1950s. During this period, a number of psychodynamic writings were published, in which infertility was considered to be the result of unconscious conflicts in the infertile woman. These conflicts included the fear of motherhood and sexuality. The *full psychogenic model of infertility* has been the main perspective on the relationship between infertility and psychological functioning in biomedicine until the 1980s [16-18]. Even when a physiological defect could be identified, the primary origin of the infertility problems was still assumed to be psychogenic in nature. Furthermore, psychological functioning of the male partner was usually not taken into consideration. As more and more somatic causes of infertility were discovered, the *full psychogenic model of infertility* got replaced by the *psychogenic model of unexplained infertility*. According to this model, all infertility difficulties for which no organic cause can be found arise from psychogenic factors. However, the results of empirical research do not affirm this model. Patients with unexplained infertility usually do not have more psychological problems than patients with somatically explained infertility [19-21].

Gradually, the focus of psychological studies in the infertility field has shifted. Nowadays, psychological problems are considered to be an effect of infertility rather than a cause. Quantitative research has shown that infertile persons experience only slightly more distress than fertile persons [22-24]. These results support the *psychological consequences model of infertility* rather than the *psychogenic model of (unexplained) infertility*, since it is highly unlikely that a moderate amount of distress can bring about infertility

problems. However, the causal relation between infertility and distress cannot be proven, since no longitudinal studies exist that follow infertile patients from before they start trying to conceive [16].

The psychological consequences of IVF treatment

Stress (or a stressor) is typically defined as a stimulus which produces mental tension or physiological arousal, whereas distress is the term used to describe the negative emotions that result from the stressor [25]. When a person appraises a situation as being stressful, they will classify it as a threat, a loss or a challenge [26]. IVF, with its painful and invasive procedures, is a burdensome treatment. Since IVF is usually the final treatment option for infertility, IVF patients have to face the possibility that they may never achieve the valuable life goal of parenthood. As such, IVF treatment poses a threat to the childless person, which may result in symptoms of anxiety. Moreover, IVF is a low-control stressor, since patients have little control over its progression and its outcome [27]. As treatment progresses and its uncontrollability continues, feelings of depression may emerge [28]. When IVF treatment fails, couples may grief over the loss of the child that was never born. The realization that their childlessness is irrevocable, may lead to the loss of an acceptable self or body image, and losses concerning self-esteem and self-confidence. Social losses may involve the ending of relationships and the loss of social status. These multiple losses related to treatment failure may evoke depressive symptoms and grief [29].

Results of quantitative research show that women who are about to start IVF may be more anxious than control populations [30-32], although in some studies no differences are found [33-35]. During treatment, women experience symptoms of anxiety, especially at oocyte pick-up and just before pregnancy testing [36, 37]. Distress levels are reported to be higher during the first and last IVF treatment cycles [31, 38, 39]. Although most women seem to adjust well to unsuccessful IVF treatment, up to 25% of women report clinically relevant levels of depression after failed IVF [40, 41]. Three years after unsuccessful IVF treatment, women report less life satisfaction, but not more distress than women who did conceive via IVF [42]. Negative emotions seem to disappear after IVF pregnancy, which could suggest that depression related to IVF treatment results from the inability to become pregnant rather than treatment itself [43]. On the other hand, the excitement and happiness associated with pregnancy may neutralize negative treatment-related emotions [See: 14].

In the Netherlands, only couples are usually eligible for IVF treatment, which makes it a dyadic stressor. Women are more likely to initiate infertility treatment than their male partners [44, 45]. Once they have started infertility treatment, women are less willing to stop treatment than men [46]. Even though men show the same pattern of emotional reac-

tions during IVF treatment as women, their emotions are usually less intense [40, 47-50]. According to Stanton and colleagues [51], there are three possible explanations for this phenomenon. One possible explanation is that the female partner has to undergo most of the invasive procedures related to IVF, regardless of which partner is infertile. Moreover, as parenthood might be a more important life goal to women [48, 52], the perceived threat posed by IVF treatment might be greater to women than to men. Finally, Stanton and colleagues [51] argue that women show a general tendency to appraise negative events as more stressful than men.

Having twins: a blessing or a burden?

Results from studies on families with twins conceived with medical assistance are in line with studies on families with naturally conceived twins. Raising two children of the same age, places huge demands on the parents. Mothers with IVF twins seem to experience more parenting stress than mothers with either naturally conceived or IVF singletons [53]. The former group also reports more dysfunctional child-parent interactions, as well as more child behaviour difficulties. Furthermore, mothers of IVF twins are less likely to be working outside the home. With every increase in multiplicity, mothers are more likely to have difficulties with meeting material family needs, such as supplies, housing and health care needs. Parents of IVF multiples may have to face intrusive questions about their children's conception status, which might cause feelings of social deviation. Moreover, mothers of IVF multiples are more likely to suffer from depression and a lower quality of life [54]. Although behavioural difficulties seem to disappear in later years, IVF twins show lower levels of cognitive functioning during their preschool years than IVF singletons [55].

Psychosocial counselling in IVF

Since the *psychological consequences model of infertility* became popular in the 1980's, professionals in the infertility field have recommended the provision of psychosocial counselling interventions to infertile patients [56]. Infertility counselling helps patients explore, understand and cope with issues related to infertility and its treatment [57]. According to the Code of Practise of the Human Fertilisation and Embryology Authority [58], several tasks of counselling can be distinguished in the context of infertility treatment. A psychosocial counsellor may help patients to collect and comprehend all information that is needed to make treatment related decisions, as well as the emotional and social implications of these decisions (e.g. implications and decision-making counselling). When IVF

treatment is causing emotional distress in patients, counsellors can offer them emotional support to help them cope more effectively with treatment strain (e.g. support counselling). Therapeutic counselling can be offered, when specific issues concerning infertility or treatment need more working through.

Although many couples embarking on IVF may welcome some form of psychosocial counselling [59], studies addressing the effectiveness of psychosocial interventions for this population are scarce. The results of the few randomized controlled studies that have been conducted in this field suggest that psychosocial counselling before or after IVF treatment does not lead to fewer post-treatment symptoms of depression and anxiety in women [60, 61]. Counselling might be more effective, when offered to patients during those stages of IVF treatment that are most stressful to them (e.g. waiting for the pregnancy test results). Furthermore, psychosocial counselling should be offered to both partners instead of individuals, as infertility is a shared problem (in the majority of cases). In this thesis, a psychosocial counselling intervention for couples undergoing their first cycle of IVF treatment was evaluated. Counselling was offered to both partners before the start of the first treatment cycle, during the waiting period and then again after completion of the first cycle.

Mild treatment strategies in IVF

Success in IVF is generally presented per cycle, which has led to complex and burdensome ovarian stimulation protocols. Adopting term live birth per time period (e.g. one year) as a new primary endpoint may encourage clinicians and scientists to develop and apply simpler stimulation protocols. Mild ovarian stimulation is likely to result in fewer physiological and psychological side effects than standard long-protocol stimulation. The introduction of GnRH antagonists has facilitated the development of such ovarian stimulation protocols for IVF [62]. In contrast to GnRH agonist treatment, the administration of GnRH antagonists can be limited to the mid to late follicular phase of the menstrual cycle. Moreover, exogenous FSH administration is limited to the mid-late follicular phase, since the endogenous inter-cycle FSH rise is exploited rather than suppressed.

Single embryo transfer (SET) offers the most reliable means of reducing the incidence of multiple pregnancies. Improved quality assessment of embryos has enhanced the effectiveness of this procedure [63]. However, the transfer of one embryo instead of two, results in a decrease in pregnancy rates per cycle. The implementation of IVF treatment strategies which combine single embryo transfer with milder ovarian stimulation protocols may allow for more IVF cycles in the same period of time, resulting in similar term live birth rate per IVF treatment. A possible drawback of milder IVF strategies, however, is the higher cycle cancellation rate and the necessity of a greater number of treatment

cycles to achieve pregnancy [64]. Establishing a high-quality cryopreservation programme for surplus embryos can provide additional pregnancy chances after transfer in subsequent cycles [65, 66].

The use of GnRH antagonists in IVF might decrease the prevalence of symptoms of depression and anxiety, which seem to be side effects of GnRH agonist ovarian suppression, possibly associated with a decline in estrogen levels [67] or a decreased serotonin density [5]. Women treated with GnRH agonist may also report menopausal symptoms, such as hot flushes and headaches [3, 4]. Indeed, mild ovarian stimulation appears to result into a smaller increase in treatment burden over cycles than standard long ovarian stimulation [68]. However, couples who fail to conceive with minimal stimulation IVF are less likely to prefer the minimal stimulation in future than pregnant couples. Likewise, most couples show more concerns about the possible higher risk of treatment failure associated with SET than about potential risks related to multiple embryo transfer [69]. Moreover, many of these couples may actually consider multiple birth to be a favourable treatment outcome, as they consider having twins as the most cost-effective means to complete their family in terms of treatment-related distress [70, 71]. More scientific evidence on the possible psychological advantages and disadvantages of the use of mild IVF strategies might change patients' preferences in favour of these strategies. This thesis describes the results of a comprehensive study of the psychological consequences of a mild IVF strategy during various stages of IVF treatment.

Stress and IVF outcome

Although nowadays most researchers would reject the *psychogenic model of infertility*, a modified version of this model is still popular in studies on IVF. The *cyclical model of stress* [16] or *stress hypothesis* [18] proposes that patients' distress has a negative influence on pregnancy chance. According to this concept, distress has a direct effect on IVF pregnancy outcome through stress-related hormones [72] or immunological mechanisms, by modulating T cell activity [73]. Also, distress is believed to have an indirect negative effect on IVF outcome through adverse health-related behaviour, such as unhealthy eating habits, smoking and alcohol consumption [74]. Smoking and overweight are known to negatively influence pregnancy rates, live birth rates and other IVF outcomes [75-78]. Alcohol intake also seems to have a negative influence on IVF outcomes, but this relationship needs to be studied further [79].

Whereas several studies suggest that distress results in reduced pregnancy rates [80-84], others have failed to find a detrimental effect of negative emotional reactions on IVF outcomes [31, 85-87]. Some authors have claimed that psychosocial interventions aimed at reducing distress increase pregnancy rates in infertile people [88, 89]. However, psy-

chosocial counseling during IVF treatment does not seem to influence IVF pregnancy rates [60, 61]. As most studies in this field show considerable limitations in study sample size and design, more large prospective studies are required. These studies should report live birth as the endpoint, as data relating to miscarriage and premature delivery are rare. In this thesis, the relationship between distress in women and live birth resulting from one cycle of IVF was studied.

Study aims and outline

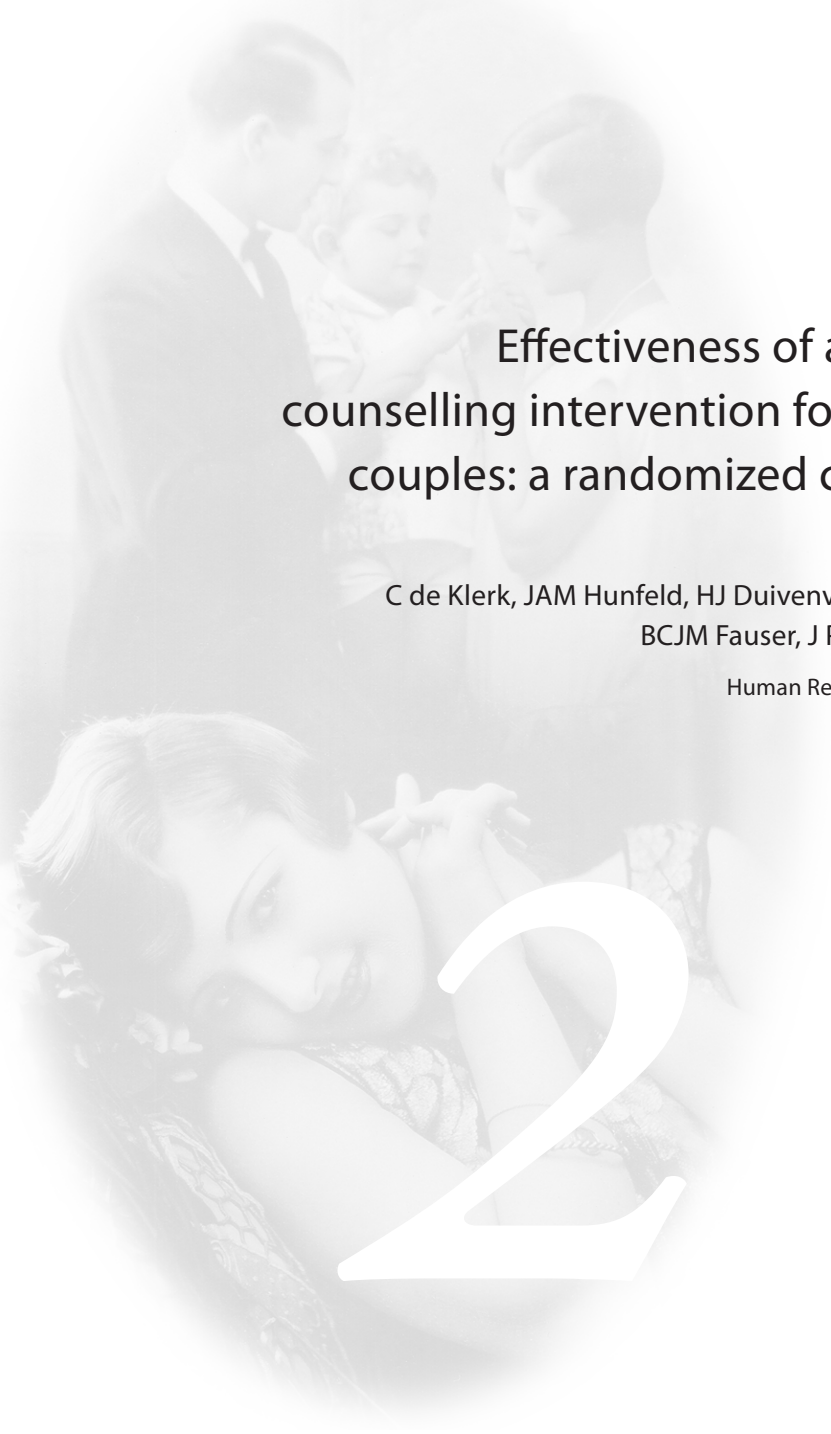
This thesis focuses on the relationship between IVF treatment and associated psychological distress in women. The main objectives of this thesis were to study patient distress both as a consequence of IVF treatment (Chapters 2-6), and as a predictor of IVF treatment outcome (Chapter 7).

In Chapter 2, a study of the effect of a psychosocial counselling intervention for couples undergoing their first cycle of IVF treatment on women's distress is presented. Women who received additional counselling by a social worker were compared with a routine-care control group in a randomized controlled trial.

In Chapters 3 to 6, studies are presented which assess whether a mild IVF strategy which combined mild ovarian stimulation with single embryo transfer results in comparable distress levels as standard IVF. In order to answer this research question, a randomized controlled trial was performed with 404 women. The methodology of this trial is described in Chapter 3. As each stage of IVF treatment might have different implications for women's psychological adjustment [31, 36, 37], distress was measured several times during treatment. In Chapter 4, distress was studied in first-time IVF patients during six separate stages of one IVF treatment cycle: ovarian stimulation, oocyte retrieval, fertilization, embryo transfer, waiting period and pregnancy testing. In Chapter 5, overall patient discomfort during a period of one year associated with both mild IVF was studied and compared with conventional treatment. Finally, Chapter 6 focuses on the impact of unsuccessful IVF treatment on women's psychological wellbeing.

Chapter 7 reports a study in which distress in women before and during a first IVF treatment cycle was prospectively examined, and its relationship to live birth delivery rates was studied. For this study, the same cohort of women was studied as in Chapters 3 to 6.

The main findings of this thesis are summarized and discussed in Chapter 8. Finally, implications for future treatment and research are given.



Chapter 2

Effectiveness of a psychosocial counselling intervention for first-time IVF couples: a randomized controlled trial

C de Klerk, JAM Hunfeld, HJ Duivenvoorden, MA den Outer, BCJM Fauser, J Passchier & NS Macklon

Human Reproduction 2005; 20: 1333-8

Abstract

BACKGROUND: The objective of this study was to evaluate a psychosocial counselling intervention for first-time IVF couples. In this article the results on women's distress are presented.

METHODS: Two hundred sixty-five couples admitted to an IVF treatment programme at the Erasmus MC were asked to participate in this study. Eighty-four couples agreed and were randomized according to a computer-generated random-numbers table into either a routine-care control group or an intervention group. The intervention consisted of three sessions with a social worker trained in experiential psychosocial therapy: one before, one during and one after the first IVF cycle. Distress was measured daily during treatment by the Daily Record Keeping Chart. Depression and anxiety were measured before and after treatment by the Hospital Anxiety and Depression Scale.

RESULTS: No significant group differences were found.

CONCLUSIONS: The results of this study do not support the implementation of our counselling intervention for all first-time IVF couples. The low response rate suggests that there is little perceived need for psychosocial counselling among couples during a first IVF treatment cycle.

Introduction

In-Vitro Fertilization (IVF) treatment can be a stressful experience to couples. The demands of treatment—daily injections, semen analysis, scans, and invasive procedures—may be a cause of distress to both partners. Additionally, many couples have to deal with treatment failure and are often confronted with emotionally difficult treatment choices, such as whether or not to freeze embryos [90]. There has been a number of clinical reports on the emotional impact of IVF treatment. Common emotional responses to infertility and its treatment are depression, anger, guilt, frustration and sadness [91]. Prospective studies have shown that women demonstrate elevated anxiety levels during IVF treatment [92, 93]. Treatment failure appears to be associated with an increased prevalence of both mild and moderate depression in both women and men [40, 94]. Indeed, anxiety and depression are considered to be causes for the relatively high drop-out rate observed after the first failed IVF cycle [95, 96]. It has also been suggested that elevated anxiety and depression may cause lower pregnancy rates [83, 84]. Most authors agree that fertility clinics should not only address the medical needs of their patients, but also their emotional needs. Boivin *et al*. [97] advocate that psychosocial counselling should be available during all stages of IVF treatment. According to the Human Fertilisation and Embryology Authority [58] the following tasks of counselling can be distinguished in the context of infertility treatment: information gathering and analysis, implications and decision-making counselling, support counselling and therapeutic counselling. Laffont *et al*. [59] suggest that many couples undergoing IVF may welcome some form of psychosocial counselling. Seventy-five percent of the participants in this study, who had been through at least one IVF attempt, expressed a wish for pretreatment counselling, while almost half of the study group requested counselling during treatment.

Despite the high agreement on the necessity of counselling IVF patients, there is a lack of studies addressing the efficacy of psychological interventions for this population. To date, only a few randomized, controlled, prospective studies have been conducted to assess the effect of counselling on distress related to infertility and its treatment. In a study by Domar *et al*. [98] infertile couples received 10 weekly sessions in either a cognitive-behavioural group or a support group. These intervention groups were not linked to an IVF programme. At six months follow-up, participants in both intervention groups showed healthier scores than the controls on several psychological variables: anxiety, marital distress, confusion, mood disturbance, stress management skills, health-promoting style and vigour. Another 6 months later, less group differences were found. Overall, the participants in the cognitive-behavioural group showed more health-promoting behaviours, especially concerning interpersonal support and stress management. Surprisingly, both subjects in this group and the control group showed less depressive symptoms than did subjects in the support group.

The study by Domar *et al*. [98] shows a long-term psychological approach to infertility. In other studies couples were offered specific support during IVF treatment. In a recent study by Emery *et al*. [61], couples were offered a pre-IVF counselling intervention in a couple format, which focused on their narrative capacities. Six weeks after the first IVF treatment cycle had ended, participation in counselling was not associated with fewer symptoms of depression and anxiety. Couples in a study by Connolly *et al*. [60] received not only a pretreatment counselling session, but also one counselling session after their first cycle of IVF treatment. Counselling was directed at difficulties associated with IVF treatment, like interpersonal and psychosexual problems. The authors concluded that counselling did not have an additional effect on anxiety or depression over information provision alone.

One possible explanation for the lack of effect of counselling in the latter two studies could be the use of general stress questionnaires as opposed to infertility-specific stress questionnaires. Furthermore, none of the above studies measured the effect of counselling on stress patients experienced during treatment, e.g. procedural stress. The aim of this study was therefore to evaluate a psychosocial counselling intervention for couples undergoing their first cycle of IVF treatment using an infertility-specific distress questionnaire. We hypothesized that counselling during the first IVF treatment cycle may reduce women's procedural distress levels during IVF treatment.

Materials and methods

Subjects

Two hundred sixty-five couples admitted to an infertility treatment programme at the Erasmus MC (Rotterdam, The Netherlands) were asked to participate in this study between June 2001 and May 2003. Inclusion criteria for this programme were: indication for IVF treatment, women aged under 41, a stable relationship and no severe psychological problems, as assessed by a physician during the couples' initial visit to the hospital. This information is gathered using a standardized protocol. Because there is some evidence that the first ever IVF treatment cycle is the most stressful to patients [31, 32], only first-time IVF patients were recruited for this study. Both partners had to be able to complete the questionnaires in Dutch. Eighty-four couples agreed to participate (32%). Reasons for non-participation are displayed in Table 2.1.

Intervention

Couples in the intervention group received three counselling sessions, each of approximately one-hour duration. Similar to Connolly *et al*. [60], we offered couples a pretreatment and a post-treatment counselling session. The pretreatment session took place

Table 2.1 Reasons for non-participation

Motivation	*n*	%
No time for counselling	57	31.5
No need for counselling	16	8.8
Discontinuation of IVF treatment	7	3.9
Work in hospital	4	2.2
Too stressed	4	2.2
No interest in study participation	2	1.1
Unknown reason	91	50.3

about one week before the first day of pituitary downregulation or the first day of ovarian stimulation (in case of GnRH antagonist co-treatment); the post-treatment session took place approximately two weeks after the day of the pregnancy test. Additionally, patients received a counselling session six to nine days after the embryo was transferred, because most IVF patients consider this stage of IVF treatment to be the most stressful. The waiting period is associated with more uncertainty and lack of control than other treatment stages [60]. All counselling sessions took place at the Erasmus MC. During the non-directive sessions couples were invited to discuss their feelings and thoughts on topics related to infertility and IVF treatment. Depending on the needs of the clients, the counsellor alternately used the four basic aspects of infertility counselling: information gathering and analysis, implications and decision-making counselling, support counselling and therapeutic counselling. Counselling was provided by a social worker who had been trained in experiential psychosocial therapy [99], which has been derived from Kempler's experiential family therapy [100]. According to this method, problems are believed to originate from an imbalance between the basic human needs autonomy and relatedness and should therefore be solved in the context of a relationship. The main goal of Experiential Psychosocial Therapy is teaching clients new (interpersonal) skills by forming not only a professional but also a personal relationship with them. Instead of being an objective observer, the counsellor expresses her own feelings and ideas about the client in order to create new interpersonal experiences for the client. It is assumed that through these personal experiences with the therapist clients learn how to cope with (inter)personal problems.

Measures

Demographics

Information on demographics and infertility history was gathered from all women by a standardized questionnaire.

Daily Record Keeping Chart (DRK)

In contrast to previous intervention studies in this area, distress was measured with an infertility-specific questionnaire, e.g. the Daily Record Keeping Chart [93, 101]. This questionnaire consists of 21 items that represent emotional reactions common to women undergoing infertility treatment. Each item is rated on a 4-point-Likert scale ('none' to 'severe'). Scores on four subscales can be obtained: depression/anger, uncertainty, positive affect and anxiety (range 0–12). The DRK showed good criterion-related validity and good convergent validity with other conceptually related scales, like the Spielberger State Anxiety Inventory [101]. However, factor analysis showed overlap between the 'negative' subscales. We therefore decided to use the General Distress Scale for this study, which combines the depression/anger, uncertainty and anxiety subscales into one negative affect scale (range 0–36). The DRK showed good internal consistency: Cronbach coefficient alpha varied from 0.76 to 0.88 for the individual subscales, while the coefficient alpha for the General Distress Scale was 0.87. The original items of the DRK were translated into Dutch.

Hospital Anxiety and Depression Scale (HADS)

To enable comparisons with other effect studies, a general stress questionnaire was also administered. The Hospital Anxiety and Depression Scale [102] was developed as a screening tool to detect anxiety and depression in medical patients. All fourteen items are scored on a 4-point-Likert scale from 0 to 3. Each of the two subscales consists of seven items (range 0–21). For this study, the Dutch version of the HADS by Spinhoven *et al*. [103] was used, which has shown good test-retest reliability, homogeneity and internal consistency. Cronbach alpha for the total scale and both subscales varied from 0.71 to 0.90. Since the total HADS scale showed a better sensitivity and positive predictive value in detecting psychiatric disorder than the two subscales, the anxiety and depression scores were also combined in a total HADS score (0–42).

Study design

The couples were randomized according to a computer-generated random-numbers table into one of two groups. Forty-one couples were randomized in a routine-care control group, forty-three couples into an intervention group. All participants completed the HADS before the couples' initial visit to the hospital (baseline). During the first week after that visit the DRK was completed daily by the women (baseline) and again daily during their first IVF cycle: depending on the ovarian stimulation protocol that was used, women started monitoring on either the first day of downregulation (GnRH agonist long protocol co-treatment) or the first day of ovarian stimulation (mild ovarian stimulation using GnRH antagonist co-treatment). Monitoring ended two weeks after the day of the pregnancy test and after the third counselling session. On that same day all participants completed the

HADS for the second time. Since previous studies have shown that men experience lower levels of distress during IVF treatment than women [50], male participants did not fill in the DRK. Results on the men's HADS scores have been reported elsewhere [104].

Procedure

The study was reviewed and approved by the Erasmus MC Ethical Review Board. Couples were informed about this study during information evenings for couples about to start their first IVF cycle at the Erasmus MC. During these meetings all couples received written information with regard to the study and the baseline HADS. In the ensuing weeks, patients who met the study criteria received a telephone call and were invited to participate in the study. Couples who agreed to take part in this study met with one of the researchers before their first medical appointment at the hospital. After the objectives of the study were discussed, both partners signed an informed consent form. The completed baseline HADS was collected and all women received a diary with one DRK for every treatment day and they were instructed to complete the DRK on a fixed moment during the day. Finally, couples were informed whether they would receive additional counselling sessions with a social worker. The questionnaire on demographics was sent by mail before the start of the first IVF treatment cycle. A second HADS was sent by mail two weeks after the first cycle had ended.

Statistical analyses

Demographical data were analysed using Student's *t*-test for continuous variables and χ^2-test for categorical variables. For the group analyses, a distinction was made between seven individual IVF treatment stages: stimulation, day of oocyte retrieval, fertilization, day of embryo transfer, waiting period, day of the pregnancy test and post-treatment. However, no results are available for the post-treatment stage, since most women discontinued monitoring with the DRK after the day of the pregnancy test. Stage scores for both positive and negative affect were calculated by averaging daily scores on the DRK within each treatment stage. In addition, the stage scores from the stimulation days until the day of the pregnancy test were averaged into two separate overall treatment scores: one for positive affect and one for negative affect. These overall treatment scores were used to get a rough estimate of the level of the overall distress of the women in our study during their first IVF treatment cycle. Due to cycle cancellation, not all women went through every of the previously mentioned treatment stages. Analyses of covariance for group comparisons for overall treatment scores were therefore adjusted for the total number of treatment stages the women passed through during their first IVF cycle. Next, analyses of covariance were conducted for group comparisons of both positive and negative affect during each individual treatment stage, adjusting for baseline affect scores. Analyses for the day of the pregnancy test and the overall treatment were also statistically

controlled for pregnancy outcome. Finally, analyses of covariance were performed for the post-treatment HADS scores on both the subscales and the total scale, controlling for the baseline HADS scores. Data analysis was performed with the couples' original group assignment (intent-to-treat design principle). Since we hypothesized that the intervention group would experience less procedural distress during the first IVF treatment cycle than controls, significance testing on all outcome measures was done at 0.05 level of significance (one-tailed). Effect sizes were measured using Cohen's d [105]. The standard deviation of the control group was used as the denominator of Cohen's d.

Results

Demographics

Non-respondents did not differ in age from women who participated in this study. Of the eighty-four couples who were recruited, forty couples (48%) discontinued participation during the study (See Figure 2.1). Twenty-four women did not return their diary, 3 couples did not want counselling anymore, 11 couples did not proceed with IVF treatment, and 2 couples required extensive counselling. The couples who completed the programme did not differ significantly from the couples who dropped out in demographics and stress as measured by the HADS at baseline. The biochemical pregnancy rate after the first IVF treatment cycle was 27% for the intervention group and 32% for the control group. This difference was not significant. Table 2.2 shows the demographic characteristics for both intervention and control groups. No significant differences were found for any of the demographic variables between groups. Six couples were not able to attend all three counselling sessions due to practical reasons.

Positive and negative affect during the first IVF cycle

Table 2.3 shows the means and 95% confidence intervals (CIs) of the DRK scores in both groups for all treatment stages individually as well as overall treatment scores for both positive and negative affect. Although overall treatment scores on negative affect were lower for the intervention group than for the control group, this difference was non-significant. Adjusting for the number of treatment stages and pregnancy outcome, group differences remained non-significant. No differences were found for the overall treatment scores on positive affect. Analyses of covariance showed that the intervention and control groups did not differ significantly on positive or negative affect during the individual treatment stages either. On the day of the pregnancy test however, the controls scored higher on negative affect than the intervention group ($P = 0.07$, one-tailed). Although this difference was not significant, the effect size (Cohen's d = 0.58) can still be considered

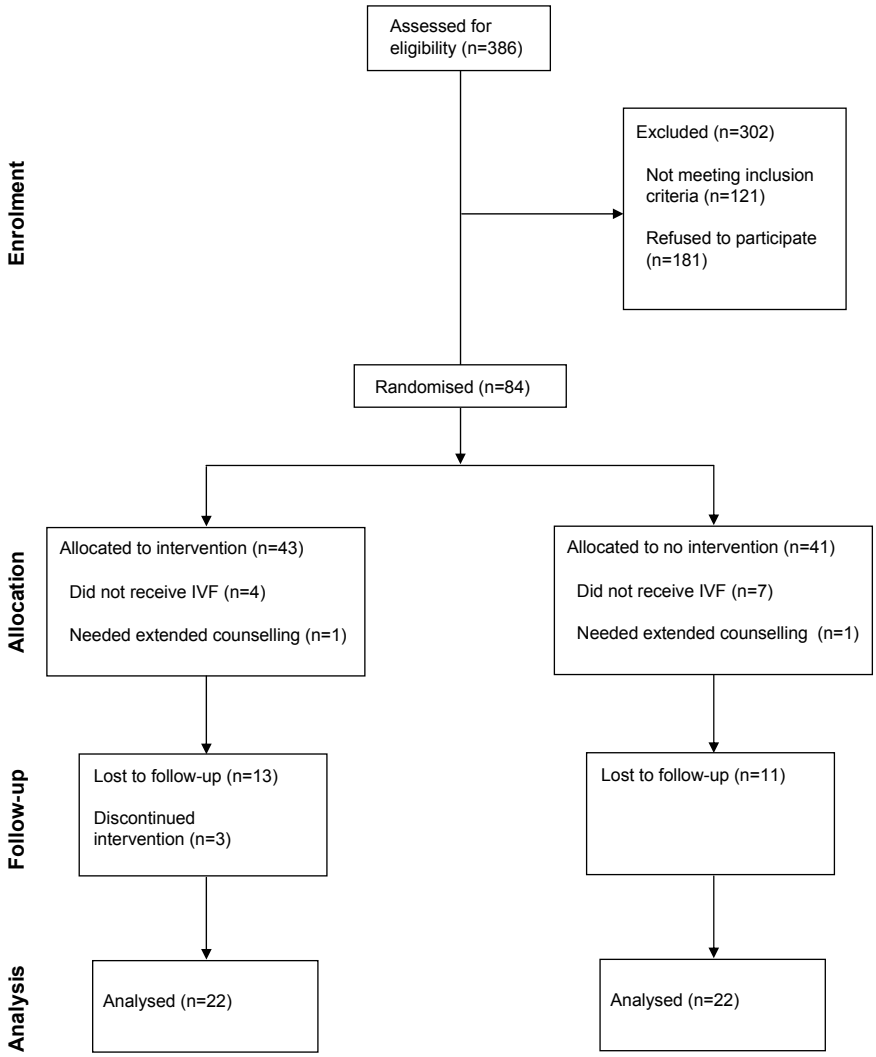


Figure 2.1 CONSORT statement flow diagram

as medium [105]. Due to the small sample size of the study, no subgroup analyses were carried out.

Anxiety and depression after the first IVF treatment cycle

No differences between the intervention (i; n = 18) and control (c; n = 15) groups were found on the depression subscale (Mi = 3.1, SDi = 2.6; Mc = 4.3, SDc = 2.6), on the anxiety subscale (Mi = 4.5, SDi = 2.6; Mc = 5.3, SDc = 2.6), or on the total scale of the HADS (Mi = 7.6, SDi = 4.5; Mc = 9.6, SDc = 4.5). Effect sizes were 0.46, 0.29 and 0.43, respectively.

Table 2.2 Demographic characteristics of intervention and control groups

Demographic variable	Intervention (n = 21)	Control (n = 19)	P[a]
Age of females (years)			
Mean (SD)	33.4 (4.7)	33.3 (5.2)	0.95
Highest level of education (%)			
Primary education	5.3	0.0	0.30
Vocational education	52.6	33.3	
Secondary education	10.5	28.6	
University etc.	31.6	38.1	
Duration of relationship (years)			
Mean (SD)	9.6 (5.3)	8.5 (5.4)	0.52
Duration of infertility (years)			
Mean (SD)	4.0 (1.7)	4.3 (3.6)	0.74
Cause of infertility (%)			
Female only	36.8	14.3	0.49
Male only	36.8	42.9	
Female and male	5.3	9.5	
Unknown cause	21.1	33.3	
One or more previous children (%)	21.1	9.5	0.40

[a] Two-tailed.

Table 2.3 Positive and negative affect assessed by the Daily Record Keeping Chart for each treatment stage

	Negative affect					Positive affect				
	Intervention		Control			Intervention		Control		
	n	M (95% CI)	n	M (95% CI)	d[a]	n	M (95% CI)	n	M (95% CI)	d[a]
Baseline	21	5.1 (± 1.4)	20	6.9 (± 2.0)	0.41	21	7.9 (± 1.2)	20	7.2 (± 1.3)	–0.24
Stimulation	21	7.7 (± 2.2)	20	7.4 (± 2.3)	–0.05	21	6.9 (± 0.8)	20	7.5 (± 0.8)	0.30
Oocyte retrieval	20	12.0 (± 3.5)	19	12.1 (± 3.6)	0.01	20	7.0 (± 1.5)	19	6.7 (± 1.5)	–0.08
Fertilization	20	11.8 (± 3.9)	18	10.9 (± 4.1)	–0.11	20	5.9 (± 1.3)	18	6.5 (± 1.4)	0.21
Embryo transfer	17	10.4 (± 4.0)	15	10.1 (± 4.3)	–0.04	17	7.9 (± 1.6)	15	8.0 (± 1.7)	0.03
Waiting days	17	11.1 (± 3.2)	15	9.3 (± 3.4)	–0.26	17	7.1 (± 1.1)	15	7.3 (± 1.1)	0.06
Pregnancy test	16	13.7 (± 5.7)	14	20.5 (± 6.1)	0.58	16	5.5 (± 1.2)	14	5.7 (± 1.3)	0.08
Overall	22	10.1 (± 2.8)	22	12.0 (± 2.8)	0.33	22	6.6 (± 1.0)	22	6.8 (± 1.0)	0.10

[a] Cohen's d as a measure of effect size: 0.2 = small; 0.5 = medium; 0.8 = large.

Discussion

The objective of the present study was to evaluate the possible effect of a psychosocial counselling intervention for couples undergoing their first cycle of IVF treatment. This intervention consisted of three sessions with a social worker during the most demanding stages of the IVF cycle. In contrast to previous studies, the effect of counselling on the procedural distress women experienced during IVF was assessed before they were aware of the pregnancy outcome. Furthermore, this was the first intervention study in which a validated infertility-specific distress questionnaire was administered, namely the Daily Record Keeping Chart. This questionnaire was expected to be more sensitive to distress related to infertility compared to the general stress questionnaires used in other studies.

Consistent with previous studies, no effect of counselling was found when stress after the first IVF cycle was measured with a general stress questionnaire (HADS). Moreover, an effect for counselling was neither found with the use of the DRK. On the day of the pregnancy test however, there was a trend towards less negative affect for women in the intervention group when compared to women who had not received counselling. Women who had received additional care seemed to be better prepared for a negative treatment outcome. Indeed, one of the goals of our counselling intervention is to reduce unrealistic expectations couples might have concerning IVF treatment outcome. Even though the difference was marginally significant, we consider it promising, since the day of the pregnancy test was the most stressful stage of treatment for both the intervention and the control groups.

The relatively low response rate of this study suggests that there is little perceived need for psychosocial support among couples during a first IVF cycle. This is in keeping with the results of a study by Boivin *et al*. [106] in which the majority of 143 infertile patients did not consider themselves to be distressed enough to need counselling. The less distressed patients in this study reported that they received sufficient support from informal sources like their spouse, family and friends. The patients who were so distressed that they wanted to consult a counsellor did not do so for practical reasons, such as the perceived difficulty of scheduling sessions. Likewise, most couples who declined to participate in our study stated that they did not have the time for three additional visits to the hospital. Although our response rate (32%) is comparable to the response rate in a study by McNaughton-Cassill *et al*. [107], Connolly *et al*. [60] were able to obtain a response rate of approximately 98%. In their study counselling sessions were combined with medical appointments. However, we intended to offer support at the most stressful treatment stages, the days before and after the pregnancy test. During these days couples do not have medical appointments. Considering our relatively low response rate, it is possible that the couples who really would have benefited from our counselling intervention did not participate in this study. In the future, effort should be made to integrate our counsel-

ling intervention into the IVF treatment to meet the needs of IVF couples. The women who did not want to participate in this study did not differ in age from the women who did agree to participate. It would be very interesting to examine further the characteristics of non-respondents in a future study. Targeting counselling interventions towards couples who have already undergone IVF treatment may be of greater benefit. The study of Laffont *et al*. [59] suggests that these couples show more interest in counselling.

Aside from the low response rate, this study also suffered from a high attrition rate. Many women did not return their diary. Additionally, many women stopped monitoring their distress after the day of the pregnancy test. Although women who dropped out of the study did not show more feelings of anxiety or depression before the start of the IVF treatment than women who did not drop out, this subgroup of women may have experienced higher levels of distress during IVF treatment. In future studies, administering the DRK for a shorter time period than in this study may prevent drop-out.

Since the low response and high attrition rate have also affected the statistical power of our study, the results of this study should be interpreted with caution. These results do not favour routine psychosocial counselling for all first-time IVF patients, a finding that is in line with the results of two previous randomized controlled studies [60, 61]. In a recent review [56], it is suggested that group interventions that focus on education and skills training (e.g., relaxation training) would be more effective than counselling interventions like the one applied in this study. However, most women in this study seemed to be able to cope with the procedural distress of their first IVF treatment without additional counselling. Since couples accepted for IVF treatment have to be in a stable relationship, it is likely that most are able to support each other during treatment or have other sources of support available to them, like family or friends. Also, the women in our study may have benefited from a supportive medical staff. Finally, it is not unlikely that the monitoring of distress itself may have had a positive effect on women's distress. It was not possible to carry out subgroup analyses due to the modest sample size of this study. One could hypothesize that benefits of counselling would be greater for those people who started the intervention with higher levels of distress. In our opinion, future research should therefore be directed at identifying couples that are particularly vulnerable to distress during their first IVF treatment cycle. Psychosocial counselling could be offered to couples who are most likely to benefit from additional support.

Acknowledgements

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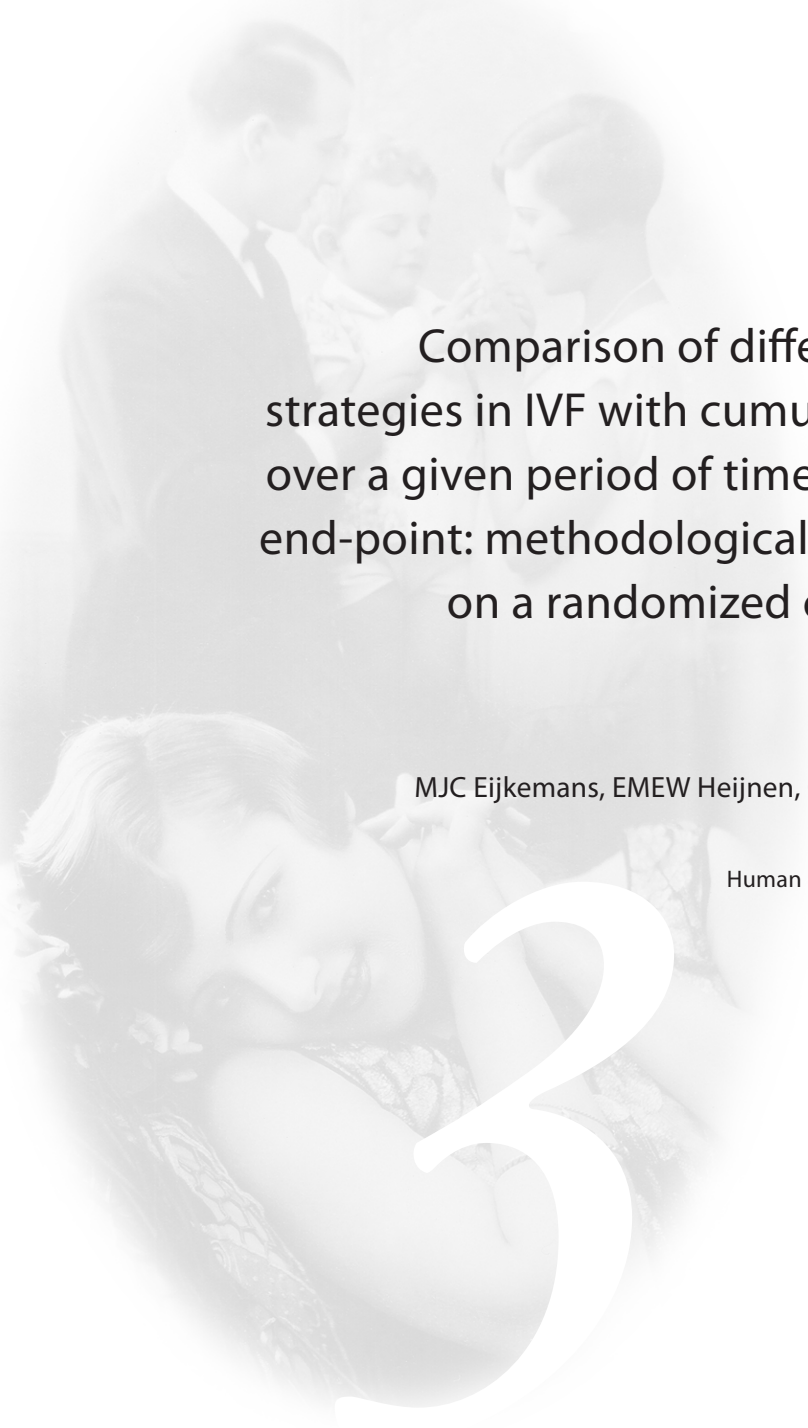

Chapter 3

Comparison of different treatment strategies in IVF with cumulative live birth over a given period of time as the primary end-point: methodological considerations on a randomized controlled non-inferiority trial

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Abstract

BACKGROUND: We discuss methodological considerations related to a study in IVF, which compares the effectiveness, health economics and patient discomfort of two treatment strategies that differ in both ovarian stimulation and embryo transfer policies.

METHODS: This was a randomized controlled clinical trial in two large Dutch IVF centres. The tested treatment strategies are: mild ovarian stimulation [including gonadotrophin-releasing hormone (GnRH) antagonist co-treatment] together with the transfer of one embryo, versus conventional stimulation (with GnRH agonist long protocol co-treatment) and the transfer of two embryos. Outcome measures are: (i) pregnancies resulting in term live birth; (ii) total costs per term live birth; and (iii) patient stress/discomfort per started IVF treatment, over a 12 month period. Power considerations for this study were an overall cumulative live birth rate of 45% for the conventional treatment strategy, with non-inferiority of the mild treatment strategy defined as a live birth rate no more than 12.5% lower compared with the conventional study arm. For a power of 80% and alpha of 0.05, 400 subjects are required.

RESULTS: As planned, from February 2002 until February 2004, 410 patients were enrolled.

CONCLUSIONS: This effectiveness study applies an integrated medical, health economics and psychological approach with term live birth over a given period of time after starting IVF as the end-point. Complete and timely patient enrolment vindicates many of the design decisions.

Introduction

The public health challenge for IVF today is to increase availability and acceptability and reduce adverse effects without compromising effectiveness. This study will address the methodological issues in designing a trial to test a less complex protocol against a common version of the standard current protocol.

IVF has been the treatment of choice in severe tubal infertility. For most other indications, IVF is applied as a last resort therapy after the failure of other treatment modalities. The high costs of the treatment, the burden of the ovarian stimulation for the patient and the complications [108], most notably the high chance of a multiple pregnancy and the associated costs, have prohibited the widespread use of IVF as a first line treatment option [64, 109]. However, the recent introduction of gonadotrophin-releasing hormone (GnRH) antagonists has opened up novel possibilities for milder stimulation protocols, which are better tolerated by the patient and less costly than the conventional stimulation regimens [110, 111]. Moreover, there is a growing awareness that the high rate of multiple pregnancies may be greatly reduced by a restricted, single embryo transfer (ET) policy [63, 65, 66, 112-114]. In theory, these developments hold promise for the future by reducing complications for both mother and child.

Single compared with dual ET has reduced success rates per fresh ET cycle, which can only be overcome by establishing a high-quality frozen-thawed embryo programme [66]. The pregnancy rates per cycle following GnRH antagonist co-treatment have been shown to be slightly, but significantly, inferior to those of the classical GnRH agonist long protocol [111]. Nevertheless, the mild stimulation approach might have advantages when evaluated over an entire (multiple cycle) treatment strategy, since the amount of time needed to complete a single IVF cycle is less and the costs of stimulation are reduced [110, 111]. More cycles could be performed on average in the same period of time for the same amount of money. Due to the better tolerability for patients, drop-out rates between cycles may be reduced, so that the number of patients reaching pregnancy within a given period of time could very well be higher compared with the conventional ovarian stimulation approach, with similar costs per pregnancy [115]. Hence, a mild ovarian stimulation protocol with GnRH antagonist co-treatment could offer a means to compensate for reduced pregnancy chances when single ET is considered. Applying such an approach, pregnancy rates will be reduced when evaluated per cycle [63, 116], but not for a given treatment period, which is more relevant to the patient. The importance of defining success of infertility therapies as live birth per treatment started instead of per cycle has been stressed recently [117]. The time has come seriously to reconsider the definition of successful IVF [112], and design future studies accordingly.

We designed a randomized controlled trial to investigate whether IVF using mild ovarian stimulation combined with single ET is not inferior in clinical effectiveness, more

patient friendly and more efficient in cost-effectiveness compared with conventional treatment. In this report, the design of the study is presented and discussed in detail.

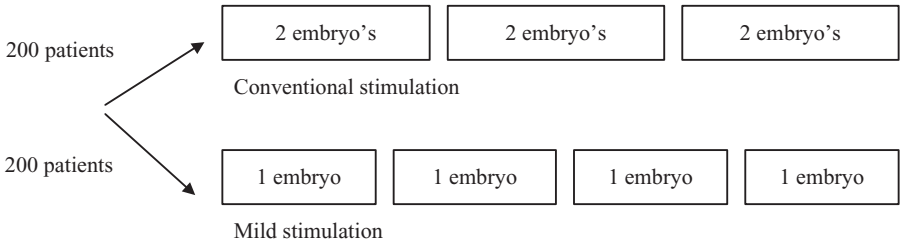
Methodological considerations

The study is designed as a two-arm randomized controlled non-inferiority effectiveness trial. The treatment strategies are mild ovarian stimulation with GnRH antagonist co-treatment along with the transfer of a single embryo versus 'conventional' ovarian stimulation combined with pituitary downregulation through the administration of a GnRH agonist long protocol, and transfer of two embryos. In brief, patients with a regular indication for IVF (with or without the addition of ICSI), female age < 38 years, normal menstrual cycle (interval between periods 25–35 days) and without severe obesity or underweight (body mass index 18–28 kg/m^2) were eligible for the study. Two academic medical centres (Rotterdam and Utrecht) participated in the study. Patient data are collected on standard patient-record forms. Patients will be followed-up for a maximum of 12 months treatment plus resulting pregnancy, until 6 weeks post-term. Analysis will be performed according to the intention-to-treat principle. The primary outcome measures are: (i) pregnancy within 1 year after randomization leading to term live birth; (ii) total costs per term live birth; and (iii) patient discomfort/distress during IVF treatment. In the following, we will describe the background of the study and justify the choices that were made in the design of the study.

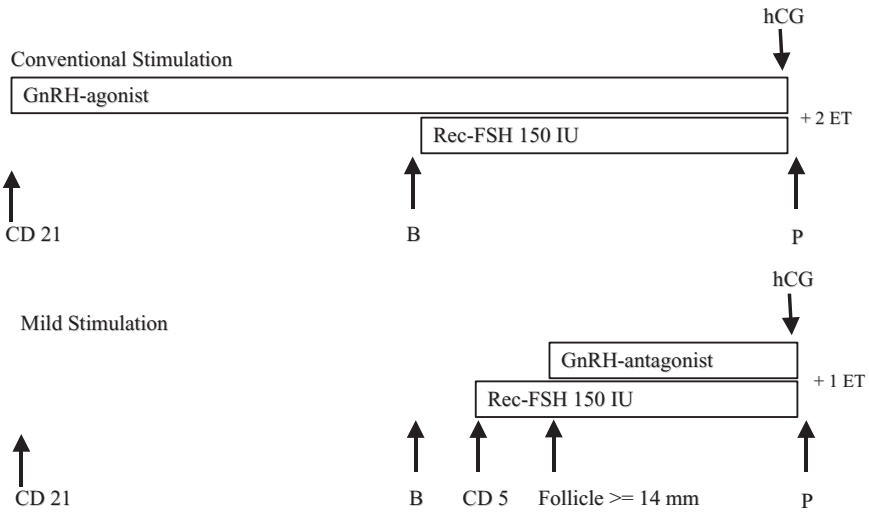
Treatment protocols

The two treatment protocols were executed in a standardized fashion, as depicted in Figure 3.1. In the conventional, GnRH agonist long protocol, two ET arm, standard ovarian stimulation is performed. After ~2 weeks GnRH agonist subcutaneously (s.c.) daily, starting during the mid-luteal phase of the pretreatment cycle (leuproline, 0.2mg/day; or triptoreline, 0.1mg/ day, depending on the clinic), ovarian stimulation is started with a starting dose varying between patients from 112.5 to 150 IU/day recombinant FSH (recFSH) s.c. The recFSH dose can be adjusted in subsequent cycles if needed. HCG 10 000 IU s.c. is administered for the induction of final oocyte maturation, when the largest follicle reaches at least 18 mm in diameter and at least one additional follicle >15 mm is observed [110]. Oocyte retrieval and fertilization are performed according to standard procedures, as described previously [118, 119]. A maximum of two (best quality) embryos is transferred [120]. Luteal phase supplementation by progesterone, 600mg/day, intravaginally is started at the evening of oocyte pick-up and continued until 12 days thereafter. In case good quality excess embryos are available, they are cryopreserved and

a) Conventional stimulation, 2 ET and the mild stimulation, 1ET arms



b) Conventional and mild stimulation protocol per cycle



CD 21: day 21 of the preceding cycle
B: day of bleeding
CD 5: day 5 of the cycle
P: day of follicle puncture for oocyte retrieval

Figure 3.1 Schematic overview of the study design

transferred in the subsequent unstimulated cycle, according to standard procedures [121]. The maximum number of IVF cycles is three.

In the mild, GnRH antagonist co-treatment, single ET arm, mild ovarian stimulation is performed by a fixed starting dose of 150 IU recFSH s.c. per day, initiated on cycle day 5. GnRH antagonist (ganirelix, 0.25mg/day; or cetrorelix, depending on the clinic) is administered s.c. if at least one follicle ≥14 mm is observed [110]. The starting day or dose

can be adjusted in subsequent cycles. Similar criteria apply for HCG, for oocyte retrieval and fertilization procedures as in the conventional group. Only the best quality embryo is transferred. Standard luteal phase support, and criteria to cryopreserve embryos will be applied as in the conventional arm. The maximum number of mild IVF cycles is four.

Background ovarian stimulation

In conventional long-protocol ovarian stimulation, the pituitary-ovarian axis is suppressed through the administration of a GnRH agonist. Subsequently, 'high dose' gonadotrophins are needed over a long period of time to let the FSH levels rise above the threshold for ovarian stimulation, and the FSH 'window' is widened for an extended recruitment of follicles. A heterogeneous cohort of follicles is recruited in this way.

In mild ovarian stimulation, natural recruitment of follicles is achieved by the inter-cycle FSH rise [122] and exogenous FSH is administered only during the mid-follicular phase, allowing more than one follicle to gain dominance [110]. This mode of stimulation interferes less with natural follicle selection and results in a lower number of aneuploid embryos, as shown recently [123].

Trial design

Effectiveness versus efficacy

The current trial is an effectiveness trial, aimed at answering the question: will the treatment strategy under consideration achieve the desired benefits in everyday routine practice? This type of trial is also referred to as a management trial [124] and should be distinguished from an efficacy or explanatory trial, which answers the question: can a treatment work under ideal circumstances [125, 126]? In an effectiveness trial, inclusion criteria and clinical protocols should resemble everyday reality. We used broad inclusion criteria and different pharmaceutical products, according to the daily routine in the two participating centres. The multi-centre design in itself leads to results that are more relevant to daily practice and less idealized than a highly controlled single centre trial.

Two versus four arms

By combining the choice between two ovarian stimulation strategies with the choice between single and dual ET, four different combinations are possible, at least in theory. The current study compares only two arms: mild ovarian stimulation and GnRH antagonist co-treatment combined with single ET versus conventional stimulation and GnRH agonist co-treatment combined with dual ET. The reason for this choice is both pragmatic (the statistical power of a four-arm trial would be much less, given the number of participants that could feasibly be recruited) as well as conceptual [the current comparison is between the conventional 'gold standard' treatment strategy in Northern Europe at the

time of design of the study [127] and a new, potentially more patient- and child-friendly integrated approach]. The possibility to perform more cycles in the same period of time (because of better patient tolerance) renders mild stimulation a suitable combination with single ET. More cycles mean additional pregnancy chances, which can compensate for the reduction in live birth rate per cycle due to the use of GnRH antagonist co-treatment along with the transfer of a single embryo. The acceptance of the proposed treatment strategies is illustrated by the timely accrual of patients into the study as depicted in Figure 3.2.

A maximum of three fresh IVF cycles was chosen in the conventional arm, for practical reasons: it is the number of cycles traditionally covered by insurance in The Netherlands. In the new treatment strategy, one extra cycle was allowed to let patients realize the potential of more cycles in the same amount of time. The cumulative number of cycles completed by the first 200 patients included is depicted in Figure 3.3.

The other two alternatives have *a priori* disadvantages: mild stimulation with dual ET might give more pregnancies over time, but does not reduce the twin pregnancy rate. Conventional stimulation with single ET does not diminish the physical and psychological burden of the conventional stimulation regime. Lower pregnancy rates have been observed [63, 116] following the transfer of fresh embryos only, and similar rates when cryo transfer is also considered [66]. A cryo policy is also applied in the current study.

Non-inferiority versus equivalence: one-sided versus two-sided testing

The study is a non-inferiority trial. A non-inferiority trial is appropriate when a new intervention has fewer adverse effects and/or lower costs, and one might accept a little

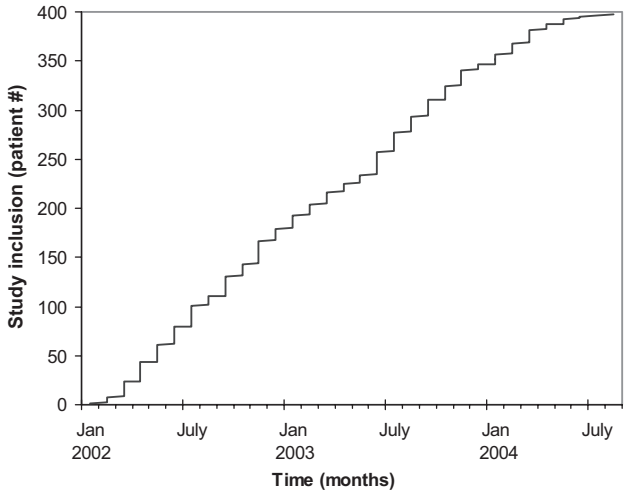


Figure 3.2 Accrual rate of the trial: cumulative number of patients included in the study against calendar time

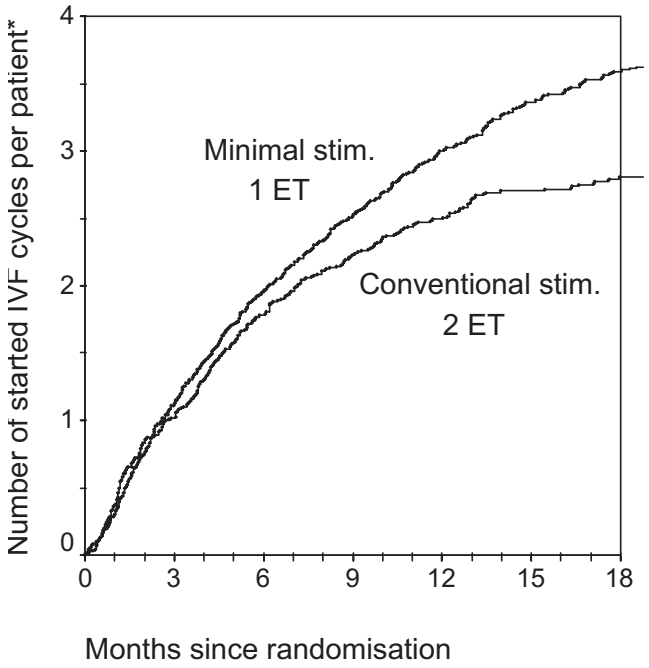


Figure 3.3 Cumulative number of started IVF cycles per patient against time since randomization, separately for the agonist two ET and antagonist one ET group. Couples who became pregnant are censored: the curve represents the theoretical number of cycles in case no one would become pregnant.

less than the benefit of the standard intervention to gain this advantage in adverse effects or costs. It is well established that the overall costs of pregnancy as well as the complications are greatly reduced by single ET, due to the elimination of twin pregnancies [109, 128-131]. If we are able to demonstrate that the mild stimulation/single ET strategy is not worse in clinical outcome compared with the conventional strategy, the reduction in multiple pregnancies with their associated higher complications and costs will become decisive in favour of the new strategy. Even if the new strategy were found to be less effective, the reduction in costs may still make it the more efficient option. Therefore, the focus in the statistical comparison will be to establish that the mild stimulation, single ET strategy is not inferior, within a predefined margin, to the long protocol, dual ET strategy, i.e. an one-sided hypothesis.

We calculated the required sample size for the study on a non-inferiority criterion derived from cost-effectiveness considerations. We used the total costs of one IVF treatment cycle of 1500 Euro from Goverde *et al.* [132], and data regarding costs of pregnancy, separately for singletons and for twins from Wolner-Hanssen and Rydhstroem [131], 5300 and 46 000 Euro, respectively, including costs of delivery, neonatal care and disability. Furthermore, we chose 45% as the total live birth rate in the conventional IVF arm (with

a maximum of three cycles), of whom 30% are twins, based on annual reports of Utrecht and Rotterdam IVF data, which are compatible with other published Dutch data [2, 133]. The expected costs per live birth would then be 26 000 Euro. We assumed that the mild stimulation, one ET strategy (with a maximum of four cycles) could have a lower cumulative live birth rate but also lower costs, due to the absence of twin pregnancies. We tested a range of differences (from –5 to –15%) in live birth rate between the new and the conventional strategy and calculated at each specified difference the costs per extra live birth of the conventional strategy compared with the experimental strategy. This cost-effectiveness ratio varied from 90 000 Euro (at a difference of –5%) to 25 000 Euro (at a –15% difference). At a difference of –12.5%, costs were 35 000 Euro. At this latter figure, we (rather arbitrarily, and only for the calculation of sample size) considered the conventional strategy no longer acceptable. Therefore, we used a difference in live birth rate between the experimental and the conventional strategy of –12.5% as the critical threshold for non-inferiority.

The number of patients should be at least 200 per arm (400 in total) to assure with 80% power that the lower boundary of the 95% one-sided confidence interval around the difference in live birth rate between the experimental and the conventional group will not fall below –12.5%, in case there is no difference in reality. The use of a one-sided alpha is allowed in this case since we have a non-inferiority trial [134]. Normally, one-sided confidence intervals are treated with disdain because they prohibit testing a treatment effect in the direction opposite to that anticipated. Here, the opposite direction would be that the new strategy is really inferior. However, it would be of no concern that the new strategy were so inferior that the difference was statistically significant: as long as the difference remains—with 95% confidence—within the predefined noninferiority margin, it is not clinically relevant.

Randomization

Block randomization, stratified by clinic, was applied to achieve balance between the two groups within each centre. Randomization was performed by sealed envelopes available at a central location in both centres. Envelopes were opened by the treating physician at the IVF intake. As appropriate for an effectiveness trial, the analysis will be according to the intention-to-treat principle, meaning that all patients will be analysed in the group into which they were randomized, whether they received the allocated treatment or not. This also applies to patients who cross over to the other treatment group. Again, this is in line with the spirit of an effectiveness trial, since in everyday practice patients may also display a preference for a treatment modality other than the one they started with.

Numerator: cumulative live birth as end-point

We defined as primary outcome a pregnancy leading to a term live birth. Term live birth is defined as live birth after a normal gestational length of 37–42 weeks. The debate is ongoing as to whether twins should be regarded as a success [112] or as a complete medical failure. From the clinical perspective, a term twin birth without complications is definitely a success. However, the increased rates of complicated deliveries, preterm births and low birth weight (all giving rise to increased chances for perinatal morbidity or mortality) associated with twin pregnancies have led to the opinion that medical intervention in infertility should preferably aim at establishing a singleton pregnancy [112]. Our choice of term live birth as primary outcome was made to give a fair advantage to healthy twin births, instead of counting all twins as a failure. In this way, the increased chance of complications of twins will be expressed in the higher rate of preterm deliveries and discounted proportionally in the outcome.

Denominator: per treatment period versus per cycle

For an effectiveness trial, the natural focus is not on the (technical) results per cycle, but rather on the overall result that a patient may expect over a given treatment period [117]. Therefore, we have chosen an analysis per treatment period, which will allow the treatment strategy that is best tolerated by the patients and requires the least amount of time per cycle, to realize more treatment cycles—thus more 'chance exposure'—than the other treatment strategy. We will use the Kaplan–Meier method, in which the usual censoring will be applied to couples who are still under treatment, but who do not yet have the maximum follow-up at the time of analysis. In contrast, drop-outs who do not wish to receive any more treatment will be assumed to have a zero chance of the outcome, i.e. a pessimistic assumption [135]. In this way, we establish a statistical penalty for drop-out due to intolerability of the treatment. The time period of analysis will start from the moment of randomization, to avoid post-randomization selective drop-out.

Health economics considerations

The economic evaluation of the study uses the societal perspective, which is central to health economics as it explicitly considers the question of how to get the most benefit from the scarce resources available to a society [136]. It implies that not only medical costs, i.e. costs made within the health care sector, should be included, but also non-medical costs, when relevant. For both medical and non-medical costs, we consider direct costs, defined as directly related to the health care problem (infertility) and treatment (IVF) under consideration, as well as indirect costs, which are made after the treatment period.

The costs of the two IVF strategies at hand can be broken down into two stages: (i) the costs of IVF treatment itself, starting with the first IVF cycle and ending with the outcome of the last IVF cycle (being pregnant, no pregnancy or drop-out); and (ii) the costs of antenatal, peripartal and post-partum care in women who have become pregnant after IVF treatment. Since the applied ET policy during treatment will affect costs during pregnancy, the cost analysis should include all costs from the start of the first IVF cycle up to and including the costs of post-partum care. Post-partum costs will be counted until 6 weeks post-term, since the term period (40 weeks gestation) is the only time horizon that is uniformly applicable to all patients. Costs are measured as the product of health care resource use ('volumes') and cost per unit estimates ('prices').

The costs of IVF treatment are broken down into direct medical costs in the hospital and outside the hospital, as well as non-medical direct costs. Direct medical costs in the hospital consist of scheduled and unscheduled out-patient visits, number of IVF cycles, personnel time per cycle, use of GnRH analogues and recFSH, costs of ultrasound and hormonal monitoring, the ET procedure and costs associated with complications. Outside hospital costs consist of GP visits, while indirect non-medical costs include travel and time costs and absence from work/sick leave due to treatment or complications. Cost volumes in the treatment stage are recorded with case record forms (CRFs), hospital-based management and budgetary information systems, patient questionnaires and the literature. Prices of hospital-based care are estimated as 'true' economic costs (including fixed costs and overheads), as variable costs and in terms of reimbursement fees. Out of hospital care is priced with reference values for The Netherlands [137]. To describe the variability in costs between the two centres, resource use and critical cost parameters are documented for each participating centre separately.

The costs of pregnancy and obstetric care can be broken down into direct medical costs in the hospital (secondary obstetric care) and direct medical costs outside the hospital (e.g. primary obstetric care, GP care, etc.). The pregnant patients will receive questionnaires covering 3 month periods of their pregnancy, regarding the out of hospital costs. The last questionnaire covers the period around the calculated term date, until 6 weeks thereafter. This means that the neonatal costs are covered for a 6 week period post-term. For preterm births, the postnatal period that we consider will therefore be extended, resulting in higher costs, as is customary in studies on neonatal care [138].

The incidence of disabilities is markedly increased in multiple pregnancies, and the associated long-term costs might be included in a cost analysis [139]. In our study, we will add the costs related to long-term health consequences in a scenario analysis, i.e. we will repeat the calculations, with projected costs of lifelong disability added to the cost analysis.

Psychological considerations

For a number of decades, outcome measures of medical interventions have not been restricted to rates on survival, mortality, morbidity and—in reproductive medicine—pregnancies, but have involved other life aspects as well. Many of these are subsumed under the denominator of 'quality of life'. Quality of life measures encompass: (i) global measures of patient satisfaction; (ii) multi-dimensional measures of health status (which often include social, psychological and physical dimensions); (iii) disease-specific measures that chart problems associated with a specific illness; and finally (iv) domain-specific measures that focus on a specific psychological outcome, such as anxiety or depression. Case reports have shown that IVF treatment is sometimes accompanied by intense moments of stress and emotional instability. Aside from being caused by physical stimuli, this emotional instability can also be attributed to the fact that patients swing between hope for a successful pregnancy and fear of failure. When choosing psychological outcomes to be included in an IVF effect study, it therefore seems essential to register negative emotions and moods, rather than assessing psychopathology.

Most psychological effect studies that have been carried out in a medical setting involved patients with a chronic disease. Often, retrospective questionnaires that cover a relatively long period of time are applied in these studies, since short-term psychological changes are less relevant in the context of chronic illness. In the case of episodic diseases or treatments (e.g. migraine and its medication), diary measures are used to monitor the day-to-day mood fluctuations that may accompany the different stages of the disease and the treatment. While the use of diary measures may reduce recollection bias [140], compliance with retrospective questionnaires may be better, as keeping a diary might be a burden to patients. In small studies, interviews are sometimes conducted to explore patients' reactions more thoroughly. Given the complexity of IVF treatment, a combination of retrospective questionnaires and diary measures would be optimal for recording both its long-term and short-term psychological effects.

Many previous studies examining the psychological consequences of IVF treatment have used depression and anxiety as their main outcome variables. These outcomes are usually measured at a few specific moments during IVF treatment (often before or after a treatment cycle) with retrospective questionnaires, such as the Spielberger's State and Trait Anxiety Inventory (STAI) and Beck's Depression Inventory (BDI). Other outcomes that are frequently measured with retrospective questionnaires in psychological IVF studies are marital adjustment and self-esteem. Aside from these general adjustment measures, some studies have used infertility-specific stress measures. The Fertility Problem Inventory (FPI), for example, measures five domains of stress that are specific to infertility: social concern; sexual concern; relationship concern; need for parenthood; and rejection of child-free lifestyle. Infertility-specific stress measures are believed to

be more sensitive to patient responses to infertility and its treatment than general stress measures. The use of standardized diaries to measure psychological variables is not widespread in the IVF field, with the exception of the Daily Record Keeping Chart [93]. This questionnaire has been developed to assess daily emotional, physical and social reactions to infertility treatment.

In the present study, a combination of retrospective and diary measures is used to ascertain both the long-term and the short-term effects of IVF treatment. During the first IVF treatment cycle, both negative and positive affect are assessed daily with the use of the Daily Record Keeping Chart, which has shown good criterion-related and convergent validity and good internal consistency [101]. Additionally, subjects are asked to fill in three retrospective questionnaires at several time points during the first treatment cycle: after randomization (baseline), on the first day of ovarian stimulation (to assess the effects of pituitary downregulation) and after embryo transfer. This last moment is considered by many patients to be the most stressful stage of IVF treatment [60]. The retrospective questionnaires are also used to measure possible psychological effects during subsequent IVF cycles. To gain insight into possible side effects related to IVF treatment, self-reported physical discomfort is measured with the somatic subscale of the Hopkins Symptom Checklist [141]. The Dutch version of the Hopkins Symptom Checklist has shown adequate to good test–re-test reliability, internal consistency and validity [142]. Additionally, subjective sleep quality is measured with the Subjective Sleep Quality Scale, a Dutch questionnaire [143], which consists of 10 items on various aspects of sleep. This scale has shown good reliability and homogeneity. Finally, stress is assessed with the Hospital Anxiety and Depression Scale (HADS), which has been developed as a screening tool to detect anxiety and depression in medical patients [102]. The Dutch version of the HADS has shown good test–re-test reliability, homogeneity and internal consistency in previous studies [103].

Discussion

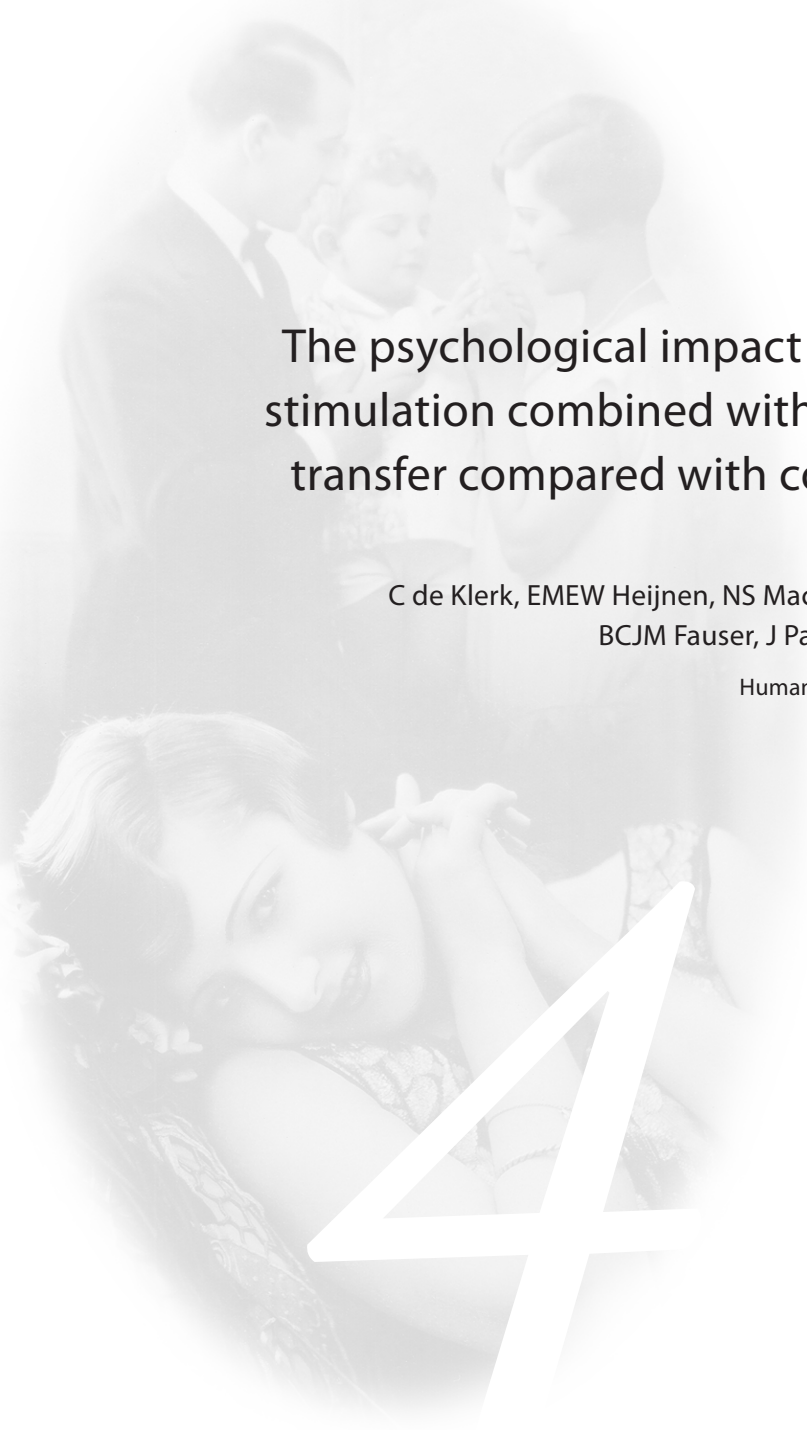
In the current report, we describe the design of a study attempting to answer the question of whether the use of a mild ovarian stimulation protocol (using GnRH antagonist co-treatment) combined with single ET is not inferior to a conventional stimulation protocol (using GnRH agonist co-treatment) with dual ET, while resulting in reduced patient discomfort and lower overall costs per pregnancy.

Success of IVF treatment has for long been focused towards technical aspects of the treatment: the number of follicles harvested, the fertilization rate or the implantation rate. The only outcome of interest to the patient, and therefore the one that should be of interest to the doctor, is whether the procedure will lead to the desired result, a healthy baby

[117, 144, 145]. All other outcome measures are no more than surrogates for this endpoint. Treatments should be evaluated against this outcome measure. A point of ongoing discussion is how to define 'healthy'. Certainly, preterm and higher order multiple births are outcomes that should be avoided if possible, but increased perinatal morbidity is also reported following twin pregnancies [112]. Should a distinction between twins versus higher order multiples be made or should only a singleton, term delivery be regarded as a success? The current study uses a term live birth as primary clinical outcome measure, which implies that adverse effects of multiple pregnancies will be reflected in a higher rate of preterm births.

In the field of infertility treatment, the chances of success come in discrete, biologically defined, portions of time, i.e. the menstrual cycle of the woman. Because of the ease of analysis and the simplicity of the cycle concept, the focus in the literature on treatment results has been almost entirely on results per cycle, particularly in IVF. An improvement seems to be the reporting of cumulative pregnancy rates per patient over multiple cycles [117]. However, as in other medical fields, the interest of the patient will be how long it will take until the desired outcome is reached. Obviously, the duration of treatment is also related to costs. Cumulative rates over a number of cycles are not very informative if it remains unknown how long it will take to finish the treatment. Thus, the concept of assessing success rates per given time interval should be considered. In our study, we hypothesized that the mild stimulation method may lead to a shorter duration of a single treatment cycle and therefore the possibility to perform more cycles in the same amount of time compared with the conventional method.

However, success rates—regardless of how this is defined— still should not be the only outcome used when comparing treatment options. The costs associated with the treatments, the patient discomfort, side effects and complications (mainly ovarian hyperstimulation syndrome and multiple pregnancies as mentioned earlier) should also be part of the equation. In the current study, we measure all these aspects in order to give an integrated evaluation of the two tested treatment strategies. In the case where one treatment strategy is comparable with the other as far as success is concerned, but with a reduced complication rate, and better in the psychological and cost dimensions, it is clearly preferable. In other cases, the costs and patient stress and discomfort will be related to the success rate in a cost-effectiveness analysis. The preferability will then depend on how high the extra costs and psychological burden of the most successful treatment strategy are per extra pregnancy. The design of this study allows all these aspects to be assessed and for a complete evaluation of two treatment strategies to be obtained.



Chapter 4

The psychological impact of mild ovarian stimulation combined with single embryo transfer compared with conventional IVF

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Abstract

BACKGROUND: The objective of this study was to assess the psychological implications of mild ovarian stimulation combined with single embryo transfer (SET) during a first In Vitro Fertilization (IVF) cycle.

METHODS: We conducted a randomized controlled two-centre trial. Three hundred and ninety-one couples were randomized to undergo either mild ovarian stimulation with GnRH antagonist co-treatment and SET (n = 199) or conventional GnRH agonist long protocol ovarian stimulation with double embryo transfer (DET) (n = 192). Women completed the Hospital Anxiety and Depression Scale, the Hopkins Symptom Checklist and the Subjective Sleep Quality Scale at baseline, on the first day of ovarian stimulation and following embryo transfer. Affect was assessed daily with the Daily Record Keeping Chart (DRK) from the first day of ovarian stimulation until the day treatment outcome became known.

RESULTS: The conventional IVF group experienced elevated levels of physical and depressive symptoms during pituitary downregulation. At oocyte retrieval, this group experienced more positive affect and less negative affect than the mild IVF group. In the conventional IVF group, cycle cancellation was associated with less positive and more negative affect.

CONCLUSIONS: During the first IVF treatment cycle, mild ovarian stimulation and SET does not lead to more psychological complaints than conventional IVF.

Introduction

Ovarian stimulation for In Vitro Fertilisation (IVF) with the use of gonadotrophin-releasing hormone (GnRH) agonist co-treatment is not without health risks. Between 0.1 and 0.5 percent of women receiving ovarian stimulation will develop ovarian hyperstimulation syndrome (OHSS) [6]. Furthermore, IVF combined with multiple embryo transfer is associated with a high incidence of multiple pregnancy [112]. In 2001, ~26% of IVF deliveries in Europe were multiples [146]. As compared to IVF singleton pregnancies, IVF twin pregnancies are associated with a higher incidence of pre-eclampsia, lower birth weight and gestational age and higher frequency of sick leave and hospitalization [147].

Apart from health risks, standard IVF treatment can be an emotional burden to patients. According to a study by Olivius *et al.* [96], psychological distress is the main reason why many patients drop out of IVF treatment before they have received all reimbursed treatment cycles. The authors reported a cumulative drop-out rate of 54% after two free cycles. Many couples have to face treatment failure, which seems to be related to an increased prevalence of subclinical anxiety and depression in women [41]. Furthermore, IVF treatment itself with its daily injections, scans and invasive procedures, such as oocyte retrieval, might be a cause of psychological distress in patients. There is some evidence that ovarian suppression with the use of GnRH agonists can cause symptoms of depression, anxiety [5] and headache [4] in patients. Multiple pregnancy may also be associated with emotional distress in parents. In a recent study, mothers with IVF multiples seemed to experience more parenting stress than mothers with either naturally conceived or IVF singletons [53].

In recent years, the clinical availability of GnRH antagonists has facilitated the development of milder ovarian stimulation protocols for IVF [62]. Milder stimulation is likely to be associated with fewer side effects and a lower risk of OHSS than standard ovarian stimulation [64]. Moreover, in a recent randomized study, pregnancy rates per started IVF cycle after mild ovarian stimulation with GnRH antagonist co-treatment were similar to a standard long GnRH agonist protocol [110]. Single embryo transfer (SET) offers the most efficient means of reducing the incidence of multiple pregnancy. Although a slightly reduced pregnancy rate per cycle may occur, similar overall pregnancy rates have been reported when the transfer of cryopreserved embryos is included [66]. However, little is known regarding the psychological disadvantages or benefits of the use of mild stimulation protocols and SET. To date, there has been one study addressing patients' satisfaction with minimal stimulation protocols [68]. In this study, patients receiving minimal stimulation (unstimulated cycle or clomiphene citrate) reported fewer side effects and stress related to hormone treatment and cycle cancellation compared to conventional stimulation. Among the minimal stimulation group, however, non-pregnant patients were less likely to prefer the same treatment protocol for future ovarian stimulation than preg-

nant patients. This suggests that patients who fail to conceive with minimal stimulation IVF start to question the effectiveness of low stimulation protocols. Likewise, most IVF couples seem to be more concerned about the possible higher risk of treatment failure associated with SET than about potential maternal, foetal and neonatal complications related to multiple embryo transfer [69]. Many infertile couples actually consider multiple birth to be a favourable treatment outcome [71]. Also, IVF patients are concerned about possible psychological and physical effects of increased length of treatment associated with SET [148]. Since the duration of GnRH antagonist co-treatment is shorter compared with treatment with GnRH agonists, the use of mild ovarian stimulation protocols might facilitate the acceptability of SET [149].

In this randomized controlled trial, potential psychological implications of mild ovarian stimulation in combination with SET were assessed. Self-reported physical and psychological complaints of women undergoing mild ovarian stimulation using GnRH antagonist co-treatment combined with SET were compared to those of women undergoing conventional IVF treatment (GnRH agonist long protocol with double embryo transfer (DET)). We aimed to ascertain whether the combination of mild ovarian stimulation and SET reduces physical and psychological complaints related to medical procedures or whether this mild approach leads to more psychological complaints related to doubts about the effectiveness of treatment. In this chapter, the results of the first treatment cycle are presented.

Materials and methods

Subjects

Between February 2002 and February 2004, women admitted to an IVF programme at the Erasmus MC (Rotterdam, The Netherlands) and the University Medical Centre (Utrecht, The Netherlands) were invited to participate in this study. To exclude women for whom either mild stimulation or SET would not be suitable, the study was limited to women aged < 38, with a regular menstrual cycle (25–35 days) and a body mass index between 18 and 28 kg/m^2 [77]. Only couples with no previous unsuccessful IVF treatment were included. Since women had to be able to read and write Dutch to complete the questionnaires, only women who spoke Dutch were selected. Three hundred and eighty-eight women agreed to participate in the study.

Intervention

Conventional stimulation with DET

In the conventional, GnRH agonist long protocol, DET group, standard ovarian stimulation was performed. After daily administering GnRH agonist subcutaneously (s.c.) (leuproline, 0.2 mg/day; or triptoreline, 0.1 mg/day) for ~2 weeks from the mid-luteal phase of the pretreatment cycle onwards, ovarian stimulation was started with a starting dose between 112.5 and 150 IU/day recombinant follicle-stimulating hormone (recFSH) s.c. Human chorionic gonadotrophin (hCG) 10 000 IU s.c. was administered to induce final oocyte maturation, when the largest follicle had reached at least 18 mm in diameter and at least one additional follicle > 15 mm had been observed. Oocyte retrieval and fertilization in vitro was performed according to standard procedures as described previously [118, 119]. A maximum of two (best quality) embryos was transferred [120]. Luteal phase supplementation with progesterone, 600 mg/day, intravaginally was started on the evening of the oocyte retrieval and continued for 12 days.

Mild stimulation with SET

In the mild, GnRH antagonist co-treatment, SET group, mild ovarian stimulation was performed with a fixed starting dose of 150 IU recFSH s.c. per day, initiated on the fifth cycle day. GnRH antagonist (ganirelix, 0.25 mg/day; or cetrorelix, 0.25 mg/day) was administered s.c. when at least one follicle ≥ 14 mm was observed [110]. Similar criteria applied for hCG, oocyte retrieval, fertilization and luteal phase support procedures as in the conventional IVF group. Only the best quality embryo was transferred [120].

Measures

Demographics

Information on women's demographics and infertility history was gathered from medical records and patient questionnaires.

Daily Record Keeping Chart (DRK)

Infertility-specific distress was measured with the DRK [93, 101]. The DRK consists of 21 items that represent emotional reactions common to women undergoing infertility treatment. Each item is rated on a 4-point-Likert scale ('none' to 'severe'). Scores on four subscales (range 0–12) can be obtained: depression/anger, uncertainty, anxiety and positive affect. The depression/anger, uncertainty and anxiety subscales can be combined into one negative affect scale (range 0–36). The DRK has shown good criterion-related validity and good convergent validity with other conceptually related scales, such as the Spielberger State Anxiety Inventory. The DRK has shown good internal consistency:

Cronbach coefficient alphas varied from 0.76 to 0.88 for the individual subscales, while the coefficient alpha for the negative affect scale was 0.87 [101]. The original items of the DRK were translated into Dutch in a previous study [150].

Hospital Anxiety and Depression Scale (HADS)

The HADS [102] was developed as a screening tool to detect anxiety and depression in medical patients. This questionnaire does not include physical symptoms of anxiety and depression, such as insomnia and weight loss, to avoid bias as a result of coexisting medical conditions. Each of the two subscales (range 0–21) of the HADS consists of seven items, which are scored on a 4-point-Likert scale from 0 to 3. Subjects were asked how they had felt during the last week. The Dutch version of the HADS [103] has shown good test-retest reliability, homogeneity and internal consistency. Cronbach alphas for the total scale and both subscales ranged from 0.71 to 0.90.

Hopkins Symptom Checklist (HSCL)

To gain insight into possible physical side effects related to IVF treatment, self-reported physical complaints were measured with the somatic subscale of the HSCL [141]. Individuals were asked to score how they had felt during the past week on eight items, which were rated on a 4-point-Likert scale from 0 ('not at all') to 3 ('extreme'). The Dutch version of the HSCL has shown adequate to good test-retest reliability, internal consistency and validity [142]. Cronbach alphas from 0.68 to 0.78 were found for this subscale, while test-retest correlation coefficients ranged from 0.71 to 0.86.

Subjective Sleep Quality Scale (SSQS)

Subjective sleep quality was assessed with the SSQS, a Dutch questionnaire [143] that consists of 10 dichotomous ('yes' and 'no') items on various aspects of sleep (e.g. 'I easily fall asleep', 'I often wake up several times during the night'). Subjects were asked to rate their sleeping problems during the past week. The SSQS has shown high reliability and homogeneity: Cronbach alphas varied between 0.84 and 0.87, while the item homogeneity coefficients (Loevingers H) ranged from 0.48 and 0.50.

Study design

This psychological study is part of a randomized controlled trial, which encompasses the medical, economical and psychological evaluation of mild ovarian stimulation combined with SET.

Four hundred and one couples were randomized according to a computer-generated random-numbers table into either the mild IVF arm (n = 205) or the conventional IVF arm (n = 196) by one of the researchers. Block-randomization, stratified by clinic, was applied to achieve balance between the two groups within each hospital. For this psychological

study, women who spoke Dutch were selected (n = 388). Women completed the HADS, the HSCL and the SSQS after they had received their stimulation schedule (baseline), on the first day of ovarian stimulation and again some days (range: 0–15) following embryo transfer. In addition, women's affect was measured daily with the DRK during 1 week at baseline and again from the first day of ovarian stimulation until the day treatment outcome became known.

Procedure

This study was reviewed and approved by the Ethical Review Boards of both participating clinics. Couples were verbally informed about the study during information evenings for couples about to start their first IVF cycle. During these meetings, all couples received written information with regard to the study. In Rotterdam, patients who met the eligibility criteria were invited to participate in the study by their fertility physician during the IVF planning consultation. In Utrecht, couples received an invitation by one of the medical researchers either on the day of their first medical appointment or during the information evening. After the objectives of the study were discussed, both partners signed an informed consent form. Randomization was carried out using sealed envelopes. Envelopes were opened by the fertility physician or one of the researchers. Women received a booklet containing the psychological questionnaires. At the time of this study, three IVF treatment cycles were covered by health insurances in The Netherlands. Couples in the mild IVF group received an additional reimbursed treatment cycle to compensate for the possible lower birth rate associated with mild ovarian stimulation combined with SET.

Statistical analyses

Demographic data were analysed using Student's t-test for continuous variables and χ^2-test for categorical variables. Analyses of covariance (ANCOVAs) were performed for the HADS scores, the HSCL scores and the SSQS scores, while controlling for the baseline scores. For the analysis of the DRK scores, a distinction was made between seven individual IVF treatment stages: baseline, ovarian stimulation, oocyte retrieval, fertilization, embryo transfer, waiting period and pregnancy test. Stage scores for both positive and negative affect were calculated by averaging daily scores on the DRK within each treatment stage. ANCOVAs were conducted for group comparisons of both positive and negative affect during each individual treatment stage, adjusting for baseline affect scores. Analyses for the day of the pregnancy test were also statistically controlled for pregnancy outcome.

To determine changes in affect over treatment for all subjects, including women whose first IVF cycle got cancelled, random effects regression analysis was conducted. Random effects regression allows for missing observations, assessments at different end-points, time-independent co-variables and time-dependent co-variables. Individual time trend

curves are based on the available data from a specific individual and data from all other subjects: intercepts represent estimated baseline functioning, while slopes characterize change in functioning over time. Since affect is strongly related to treatment outcome, the first treatment cycle was divided into periods: the period before treatment outcome was known (from baseline until the waiting days) and the day that treatment outcome became known.

In the random effects regression analyses for stage scores from baseline until the waiting period, both dependent variables (negative affect and positive affect) were modelled on the basis of a random intercept term, a random effect representing time (stage) in treatment, and fixed effects representing treatment (mild IVF versus conventional IVF) and cancellation (yes or no). In a second series of random effects regression analyses, both dependent variables were modelled on the basis of a random intercept term, a random effect representing time (before versus after treatment outcome) in treatment, and fixed effects representing treatment (mild IVF versus conventional IVF), pregnancy (no versus yes), and cancellation (no or yes). Interaction terms were entered into the models if it made sense both clinically and statistically. All models were adjusted for the time-independent co-variable hospital (Rotterdam versus Utrecht) and were fitted using restricted maximum likelihood measures. The covariance matrix was specified as unstructured (general covariance). All analyses were performed using the Statistical Package for the Social Sciences (SPSS version 10.1), while random effects regression models were implemented with the PROC MIXED procedure of SAS System (version 8.2). Significance testing on all outcome measures was done at 0.05 level of significance (two-tailed). Effect sizes were measured using Cohen's d [105]. The standard deviation (SD) of the conventional IVF group was used as the denominator of Cohen's d.

Results

Demographics

Of the 388 couples that were recruited, 29 couples did not receive their allocated intervention (See Figure 4.1). Table 4.1 shows the demographic characteristics for the remaining women in both the mild and the conventional IVF group. No significant differences were found for any of the demographic variables between groups. Twenty-six women failed to return their psychological questionnaires. Drop-outs did not differ from participants on most demographics, with the exception of the number of previous children. Of the drop-outs, 25.5% (12 out of 47) had one or more children of their own at the time they started treatment, while 13.3% (37 out of 278) of the participants were parents.

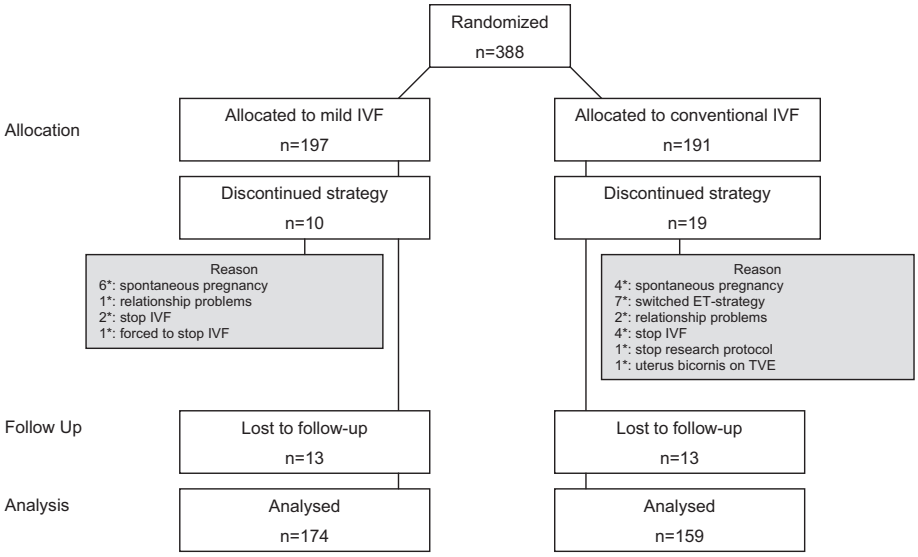

Figure 4.1 CONSORT statement flow diagram. ET = embryo transfer; TVE = transvaginal echoscopy

Psychological and physical complaints related to pituitary downregulation

Table 4.2 shows the adjusted means and 95% confidence intervals (CIs) of the scores on the HADS, the HSCL and the SSQS for both the mild and the conventional IVF group at three points during the first IVF treatment cycle. To assess the possible physical and psychological complaints related to downregulation, group comparisons (ANCOVA) were made for all scores on the first day of ovarian stimulation. Women in the conventional IVF group reported more depressive symptoms ($P < 0.01$, two-tailed) and more physical discomfort ($P < 0.01$, two-tailed) in the week before the first day of ovarian stimulation (last week of downregulation) than women in the mild IVF group (no downregulation). In that week, women undergoing pituitary downregulation reported more frequent headache, lower back pain and muscle pain than women in the control group. Effect sizes of these differences were small (Cohen's d = 0.43) and medium (Cohen's d = 0.57), respectively. Exploratory analyses showed that 5.2% (8 out of 154) of women in the conventional IVF group scored above the cut-off score for *probable* depressive disorder against 2.4% (4 out of 170) of women in the control group.

Psychological and physical complaints during each individual IVF stage

In Table 4.3, the adjusted means and 95% CI of the DRK scores are shown for both groups for each individual treatment stage. ANCOVAs showed that the mild and the conventional IVF groups did not differ significantly on positive or negative affect for most individual treatment stages, with the exception of the day of oocyte retrieval. On this day, women in the mild IVF group scored higher on negative affect ($P = 0.03$, two-tailed) and lower

Table 4.1 Demographic characteristics of mild and conventional IVF groups

Demographic variable	Mild IVF (*n* = 187)	Conventional IVF (*n* = 172)
Age (years)		
Mean (SD)	33.0 (2.9)	32.7 (3.3)
Duration of wish for a child (years)		
Mean (SD)	3.6 (1.9)	3.6 (2.1)
Duration of infertility (years)		
Mean (SD)	3.9 (2.0)	3.6 (2.0)
Cause of infertility (%)		
Female	19.8	25.0
Male	49.2	52.3
Female and male	5.3	4.7
Unknown cause	25.7	18.0
One or more previous children (%)	17.6	14.6
Highest level of education (%)	(*n* = 173)	(*n* = 159)
Primary education	0.6	3.1
Secondary education	63.0	61.0
Higher education	36.4	35.8

on positive affect ($P = 0.01$, two-tailed) than women in the conventional IVF group. However, the effect sizes of these differences were small (Cohen's d = –0.28 and Cohen's d = 0.32, respectively). No group differences were found on HADS, HSCL and SSQS scores during the waiting days.

Positive and negative affect over time (first IVF cycle)

The results of the random effects regression analyses evaluating changes in positive and negative affect from baseline until the waiting period are presented in Table 4.4. For positive affect, a significant effect for *treatment by cancellation* was found ($P < 0.01$). Women in the conventional IVF group whose first treatment cycle got cancelled experienced less positive affect during treatment than women in the mild IVF group with a cancelled first cycle. Significant effects for *time* were found for both positive and negative affect. The day of oocyte retrieval was associated with more negative and less positive affect than other treatment stages.

In Table 4.5, the results are presented of the random effects regression analyses evaluating changes in positive and negative affect from the period before treatment outcome to the day that treatment outcome became known. For positive affect, a significant effect for *treatment by cancellation* was found ($P < 0.01$). Women in the conventional IVF group with a cancelled first cycle experienced less positive affect on the day their treatment was cancelled than women undergoing mild IVF. For negative affect, a significant effect for *time by treatment* was found ($P < 0.01$). Women undergoing conventional IVF

Table 4.2 Adjusted means (M) and 95% confidence intervals (CI) of depression, anxiety (HADS), physical discomfort (HSCL) and subjective sleep quality (SSQS) at intake (baseline), before the initiation of ovarian stimulation (T1) and after embryo transfer (T2) of the first IVF cycle, and effect sizes (d)

	Baseline					T1					T2				
	Mild IVF		Conventional IVF			Mild IVF		Conventional IVF			Mild IVF		Conventional IVF		
	n	M (95%CI)	*n*	M (95%CI)	d[b]	*n*	M (95%CI)	*n*	M (95%CI)	d[b]	*n*	M (95%CI)	*n*	M (95%CI)	d[b]
Depression	168	2.8 (± 0.4)	152	2.3 (± 0.4)	-0.21	162	2.6 (± 0.3)	119	3.5 (± 0.4)[a]	0.43	99	3.5 (± 0.6)	101	4.1 (± 0.5)	0.21
Anxiety	168	5.1 (± 0.6)	152	4.8 (± 0.5)	-0.09	162	5.0 (± 0.5)	120	5.4 (± 0.5)	0.16	99	5.5 (± 0.7)	101	6.1 (± 0.7)	0.18
Physical discomfort	169	2.0 (± 0.3)	150	2.1 (± 0.3)	0.04	163	2.0 (± 0.3)	118	3.2 (± 0.4)[a]	0.57	98	2.9 (± 0.5)	100	3.1 (± 0.5)	0.05
Sleep quality	169	8.7 (± 0.2)	150	8.5 (± 0.3)	0.07	162	8.4 (± 0.2)	119	8.3 (± 0.3)	0.08	98	7.9 (± 0.4)	97	7.8 (± 0.4)	0.07

[a] Significant group difference ($P < 0.05$, two-tailed).

[b] Cohen's d as a measure of effect size: 0.2 = small; 0.5 = medium; 0.8 = large.t

Table 4.3 Adjusted means (M) and 95% confidence intervals (CI) of positive and negative affect (DRK) for the individual stages of the first IVF cycle, and effect sizes (d)

	Negative affect					Positive affect				
	Mild IVF		Conventional IVF			Mild IVF		Conventional IVF		
	n	M (95% CI)	*n*	M (95% CI)	d[b]	*n*	M (95% CI)	*n*	M (95% CI)	d[b]
Baseline	154	5.6 (± 0.7)	140	5.0 (± 0.7)	-0.13	154	7.7 (± 0.5)	140	7.8 (± 0.5)	0.03
Stimulation	141	7.0 (± 0.8)	133	6.7 (± 0.8)	-0.05	141	7.2 (± 0.3)	133	7.1 (± 0.3)	-0.04
Oocyte retrieval	119	12.4 (± 1.0)	138	10.8 (± 0.9)[a]	-0.28	119	5.4 (± 0.5)	136	6.2 (± 0.5)[a]	0.32
Fertilization	124	8.0 (± 0.9)	139	8.2 (± 0.8)	0.13	124	6.1 (± 0.4)	137	6.3 (± 0.4)	-0.09
Embryo transfer	108	8.3 (± 0.9)	124	8.7 (± 0.9)	0.00	108	7.1 (± 0.5)	120	7.6 (± 0.4)	0.17
Waiting days	103	8.4 (± 0.8)	113	8.9 (± 0.8)	-0.07	103	6.1 (± 0.5)	110	6.0 (± 0.5)	-0.07
Pregnancy test	84	15.0 (± 2.1)	92	17.6 (± 2.0)	0.26	84	4.1 (± 0.6)	92	4.2 (± 0.6)	0.04

[a] Significant group difference ($P < 0.05$, two-tailed).

[b] Cohen's d as a measure of effect size: 0.2 = small; 0.5 = medium; 0.8 = large.

Table 4.4 Random effects regression models for positive and negative affect (DRK) from intake until the waiting days

	Positive affect b[a] (95% CI)	Negative affect b[a] (95% CI)
Intercept	5.7 (± 0.6)[b]	9.4 (± 1.2)[b]
Stage: baseline	1.7 (± 0.3)[b]	-3.5 (± 0.7)[b]
Stage: stimulation	1.0 (± 0.3)[b]	-1.9 (± 0.7)[b]
Stage: oocyte retrieval	-0.1 (± 0.3)	2.6 (± 0.7)[b]
Stage: fertilization	0.2 (± 0.3)	-0.6 (± 0.7)
Stage: embryo transfer	1.5 (± 0.3)[b]	-0.2 (± 0.7)
Stage: waiting days	0.0 (± 0.0)	0.0 (± 0.0)
Treatment (0=SET, 1=DET)	0.6 (± 0.7)	-0.8 (± 1.2)
Cancellation (0=no, 1=yes)	0.5 (± 1.1)	0.5 (± 1.7)
Hospital (0=Rotterdam, 1=Utrecht)	0.0 (± 0.6)	-0.7 (± 1.2)
Time x treatment		
Treatment x cancellation	-2.6 (± 1.8)[b]	

[a] b = unstandardized regression coefficient.

[b] Significant effect ($P < 0.05$).

SET = single embryo transfer; DET = double embryo transfer.

Table 4.5 Random effects regression models for positive and negative affect (DRK) from before until after treatment outcome

	Positive affect b[a] (95% CI)	Negative affect b[a] (95% CI)
Intercept	6.6 (± 0.6)[b]	8.1 (± 1.3)[b]
Time (0=before outcome, 1=after outcome)	-4.6 (± 0.4)[b]	10.9 (± 1.0)[b]
Treatment (0=SET, 1=DET)	0.6 (± 0.6)	0.1 (± 1.5)
Pregnancy (0=no, 1=yes)	-0.6 (± 0.7)	2.0 (± 2.3)
Cancellation (0=no, 1=yes)	0.7 (± 1.0)	0.4 (± 1.8)
Hospital (0=Rotterdam, 1=Utrecht)	0.1 (± 0.6)	-0.5 (± 1.3)
Time x treatment		1.7 (± 1.4)[b]
Time x pregnancy	6.3 (± 0.6)[b]	-9.9 (± 1.6)[b]
Treatment x pregnancy		-2.6 (± 2.9)
Treatment x cancellation	-3.0 (± 1.7)[b]	

[a] b = unstandardized regression coefficient.

[b] Significant effect ($P < 0.05$).

SET = single embryo transfer; DET = double embryo transfer.

experienced more negative affect on the day treatment outcome became known than the mild IVF group. Significant effects were found for *time* and *time by pregnancy* for both positive and negative affect. Women experienced more negative and less positive affect on the day treatment outcome became known than during treatment, especially women who were not pregnant.

Discussion

The objective of this study was to investigate whether mild ovarian stimulation in combination with SET represents a more patient-friendly alternative for conventional IVF treatment. In this study, pituitary downregulation with GnRH agonist was associated with elevated levels of physical discomfort. Women who were undergoing pituitary downregulation more frequently reported symptoms such as headache, abdominal pain and sore muscles, in the week before the start of ovarian stimulation compared to the control group. During subsequent treatment stages, however, no differences were found with regard to physical discomfort between the two study groups. This suggests that *mild* ovarian stimulation might not be milder in terms of experience for the patient. Since the average cycle duration is shorter for mild stimulation protocols, patients suffer from physical complaints for a shorter period of time.

In line with previous research [5], pituitary downregulation with GnRH agonist was associated with elevated levels of symptoms of depression in the current study. However, average depression scores did not reach the cut-off score defining clinical depression in either group. Furthermore, the percentage of women that showed *probable* depression disorder was just a little higher in the conventional IVF group than in the control group. During most corresponding treatment stages, women in the mild IVF group did not differ from the conventional IVF group in terms of self-reported psychological symptoms. At oocyte retrieval, however, the mild IVF group showed significantly more negative and less positive affect than women undergoing conventional IVF. It must be noted that the clinical relevance of this finding might be limited, since effect sizes of these differences were small. Nonetheless, there might be a change of attitude needed in the way fertility physicians view the mild IVF approach. Since some of the fertility physicians were a little sceptical about the mild stimulation protocol, it is possible that these physicians were more inclined to show negative reactions towards mild IVF patients at oocyte pick-up. Furthermore, patients receiving mild IVF might have compared their results with the results of patients who were treated with standard IVF treatment which might also have influenced how patients in the mild IVF group perceived their chance of success. In future, information provision about expected results throughout treatment might reduce concerns about effectiveness in patients.

Consistent with the findings of Højgaard *et al.* [68], the results of this study suggest that cycle cancellation is associated with a less positive and a more negative mood in women undergoing conventional IVF than in women who undergo mild IVF. When cycle cancellation occurs, women undergoing mild IVF have usually been through a few days of ovarian stimulation only. Women in the conventional IVF group, on the other hand, have already invested much more in their treatment at that time. Aside from a few days of ovarian stimulation, they have also been through 1–2 weeks of medication in order

to achieve pituitary downregulation. Another explanation for this finding could be the fact that women undergoing mild stimulation were offered a maximum of four instead of three reimbursed cycles in conventional IVF.

The attrition rate of the study was just 14.2% (55 out of 388). After randomization, seven couples in the conventional IVF group preferred SET to DET. None of the couples that were randomized into the mild IVF group changed their minds about having SET before treatment had started. Only 26 women failed to return their booklet with questionnaires. Not all women who did return their booklet provided scores on all time points, probably because of the complexity and the frequency of the measurements. This might have led to an underestimation of symptoms, since one could hypothesize that filling in questionnaires would have been a greater burden to women who were experiencing more symptoms.

Another limitation of this study is that no records were kept on non-respondents. It is therefore not entirely clear how representative the study group is for all patients that are eligible for mild ovarian stimulation combined with SET. Based on the average number of couples which undergo IVF treatment annually in the two participating hospitals and who would qualify for the study (n = 300), the estimated response rate is 64.7% (388 out of 600). This estimated number of patients who were willing to undergo SET is relatively high in comparison with other studies on patient attitudes towards SET. In a study by Pinborg *et al.* [151], for example, only 25% of 870 interviewed IVF mothers would agree to SET. However, 25% of these women would reconsider accepting SET, if offered more than the usual number of covered treatment cycles. In the present study women in the mild IVF group were offered four reimbursed treatment cycles instead of the usual three, which may have been an incentive to participate.

One could expect that psychological complaints in women undergoing mild IVF would only emerge after a negative treatment outcome. In the study by Højgaard *et al.* [68], patients undergoing minimal ovarian stimulation were less likely to prefer the same treatment protocol for future ovarian stimulation after treatment failure. In the current study, women in the mild IVF group actually experienced less negative affect on the day of pregnancy test than women in the conventional IVF group, although this difference was only marginally significant. Future research is needed to study psychological consequences of mild IVF during later cycles. What if overall treatment fails? Maybe then women will start wondering whether or not they chose the best treatment protocol available.

In conclusion, these first results suggest that mild stimulation in combination with SET represents a patient-friendly alternative for conventional IVF. Mild stimulation protocols circumvent the need for pituitary downregulation, which is associated with symptoms of depression, headache, lower back pain and muscle pain. Possible concerns with regard to the effectiveness that may arise during treatment (especially around the day of oocyte

retrieval) might be reduced if objective information concerning treatment and expected results is provided during all stages of treatment.

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Chapter 5

A mild treatment strategy for in-vitro fertilisation: a randomized non-inferiority trial

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Abstract

BACKGROUND: Mild in-vitro fertilization (IVF) treatment might lessen both patients' discomfort and multiple births, with their associated risks. We aimed to test the hypothesis that mild IVF treatment can achieve the same chance of a pregnancy resulting in term live birth within 1 year compared with standard treatment, and can also reduce patients' discomfort, multiple pregnancies, and costs.

METHODS: We did a randomized, non-inferiority effectiveness trial. 404 patients were randomly assigned to undergo either mild treatment (mild ovarian stimulation with gonadotropin-releasing hormone [GnRH] antagonist co-treatment combined with single embryo transfer) or a standard treatment (stimulation with a GnRH agonist longprotocol and transfer of two embryos). Primary endpoints were proportion of cumulative pregnancies leading to term live birth within 1 year after randomization (with a non-inferiority threshold of −12.5%), total costs per couple up to 6 weeks after expected date of delivery, and overall discomfort for patients. Analysis was by intention to treat. This trial is registered as an International Standard Randomized Clinical Trial, number ISRCTN35766970.

FINDINGS: The proportions of cumulative pregnancies that resulted in term live birth after 1 year were 43.4% with mild treatment and 44.7% with standard treatment (absolute number of patients = 86 for both groups). The lower limit of the one-sided 95% CI was −9.8%. The proportion of couples with multiple pregnancy outcomes was 0.5% with mild IVF treatment versus 13.1% ($P < 0.0001$) with standard treatment, and mean total costs were € 8333 and € 10 745, respectively (difference € 2412, 95% CI 703–4131). There were no significant differences between the groups in the anxiety, depression, physical discomfort, or sleep quality of the mother.

INTERPRETATION: Over 1 year of treatment, cumulative rates of term live births and patients' discomfort are much the same for mild ovarian stimulation with single embryos transferred and for standard stimulation with two embryos transferred. However, a mild IVF treatment protocol can substantially reduce multiple pregnancy rates and overall costs.

Introduction

In-vitro fertilisation (IVF) is a complex treatment for infertility that entails costly regimens for ovarian stimulation [7], serious discomfort to patients [64] and substantial risks of complications [6, 112]. Ovarian stimulation protocols aim to generate many oocytes to compensate for inefficiencies in laboratory procedures and to generate several embryos for transfer into the uterus. Conventional ovarian stimulation protocols include co-treatment with gonadotropin-releasing hormone (GnRH) agonists, to desensitise the pituitary gland [152]. By contrast, GnRH antagonists can be administered on only those days in the mid-to-late follicular phase of the menstrual cycle during which there is a risk of a premature rise in luteinising hormone (LH). This method allows the endogenous intercycle rise in follicle-stimulating hormone (FSH) to be utilised rather than suppressed [122]. Mild stimulation protocols, in which exogenous FSH is given only in the mid-to-late follicular phase, have been shown to be feasible for stimulation of growth of several dominant follicles for IVF [64, 110]. Although reduction in effectiveness per cycle is a potential drawback of co-treatment with GnRH antagonists [111, 153], mild stimulation protocols could also lessen patients' discomfort by diminishing symptoms associated with pituitary downregulation [64]. The resultant reduction in drop-outs could create additional pregnancy chances in subsequent IVF cycles [96].

Because (higher-order) multiple pregnancies are associated with increases in infant mortality and morbidity, they are seen as the most important complication of IVF treatment [112]. The financial effect of multiple births on health-care resources has been shown to be greater than the cost of IVF treatment itself [109, 154]. Multiple pregnancies due to IVF treatment can be avoided by transfer of a single embryo [155]. The reported decrease in the chance of pregnancy per cycle after single embryo transfer could possibly be overcome by establishment of a high-quality cryopreservation programme for surplus embryos (which would provide additional pregnancy chances in subsequent cycles) [66], or by additional IVF cycles [156]. A growing number of northern European centres offer single embryo transfer as standard practice for young women [157]. However, widespread implementation of single embryo transfer is hindered by a perceived need to ensure the maximum chance of pregnancy per cycle [115].

Strategies with shorter ovarian stimulation protocols (such as GnRH antagonist co-treatment) and transfer of a single embryo could allow more IVF cycles in the same period as conventional treatment, and produce a similar proportion of term live births, despite a minor reduction in the proportion of term live births per treatment cycle. Moreover, mild strategies could reduce patients' discomfort and diminish costs associated with multiple pregnancies. We aimed to test this hypothesis—i.e., that a mild IVF protocol could produce a similar proportion of term live births to conventional treatment in the same period, and also reduce patients' discomfort, multiple pregnancies, and total costs per couple [158].

Methods

Participants and study design

We recruited patients with an indication for IVF or intracytoplasmic sperm injection on the basis of tubal, male, or unexplained infertility at two academic medical centres in Rotterdam and Utrecht between February, 2002, and March, 2004.18 Eligible patients had had no previous IVF treatment or had borne a healthy child after previous IVF treatment, were aged younger than 38 years, and had a menstrual cycle length of 25–35 days and a body-mass index of 18–28 kg/m^2 [158].

This study was designed as a parallel-group randomized, open-label, non-inferiority effectiveness trial [158]. The study protocol was approved by the local ethics review committee of the Erasmus Medical Centre, Rotterdam, and the University Medical Centre, Utrecht. Written informed consent was obtained from all patients before they were randomly assigned to mild or standard treatment groups. To compensate for a possible reduction in probability of pregnancy per IVF cycle, patients in the mild treatment group were offered reimbursement of one extra cycle in addition to the three cycles normally reimbursed in the Netherlands. We estimated that within 1 year of the start of treatment, most patients undergoing standard treatment could complete up to three cycles, whereas those undergoing the shorter mild treatment could complete up to four cycles [158].

Procedures and assessment

The randomization sequence was computer-generated; random blocks of size four and six were stratified by centre to maintain balance between the two treatment groups within each centre. The resultant sets of treatment assignments were put into numbered sealed envelopes and made available at each centre; envelopes were sequentially allocated to consecutive patients and opened by treating physicians at IVF planning consultations.

One treatment group was given mild ovarian stimulation, consisting of GnRH antagonist co-treatment, combined with single embryo transfer, and the other was given standard ovarian stimulation with the GnRH agonist longprotocol, combined with transfer of two embryos [158]. Supernumerary high-quality embryos were cryopreserved and thawed for transfer in a subsequent unstimulated cycle before the start of a new IVF treatment cycle. These frozen-thawed embryo-transfer cycles were treated as a part of the previous IVF cycle. In both groups either one or two cryopreserved embryos were transferred, according to the patient's preference. Intervals between IVF cycles were determined by logistic reasons and patients' preference. Patients were treated by independent physicians.

The costs of the two IVF strategies for the financial year 2004 were divided into two stages: treatment itself, up to the outcome of the last IVF cycle, and antenatal, peripartum, and postpartum care until 6 weeks after the expected delivery date in women who conceived within the treatment period [158]. Costs of miscarriages and ectopic pregnancies

were also taken into account. Data on resource use were collected for each individual from case-record forms and questionnaires. Real medical costs were calculated from a societal perspective, by use of the microcosting method [159].

The Hospital Anxiety and Depression Scale (range 0–21), the somatic subscale of Hopkins Symptom Checklist (range 0–24), and the Subjective Sleep Quality Scale (range 10–0), were used to assess patients' stress (anxiety and depression), physical discomfort, and sleep quality, respectively [158]. Women completed these questionnaires at baseline (just after randomization), directly after the first embryo transfer, and 1 week after the outcomes of subsequent cycles (such as cancellations or pregnancy tests) [158]. For assessment of patients' discomfort, the areas under the cumulative score within 12 months were compared between study groups by use of ANCOVA, after adjustment for baseline scores.

Primary outcome measures were pregnancy and term live birth within 1 year of randomization; total costs per couple and child up to 6 weeks after expected delivery; and patients' discomfort [158].

Statistical analysis

200 patients per group were needed to assure with 80% power that the lower limit of the 95% one-sided CI for the difference in the proportion of term live births was within a prespecified non-inferiority boundary of 12.5% [158]. The standard treatment strategy was assumed to have a 45% cumulative chance of success [158]. Data were analysed according to the principle of intention to treat. All pregnancies within 1 year of randomization were analysed, whether achieved by IVF, cryopreservation, intrauterine insemination, or spontaneous conception. To ensure that the comparison of treatment strategies was not affected by patients who changed to a different stimulation protocol or embryo-transfer policy, another analysis was done without these patients. The Kaplan-Meier method was used to calculate the 1-year cumulative proportion of pregnancies leading to term live births; patients who withdrew from IVF treatment were not censored. Spontaneous pregnancies after patients withdrew from treatment were included in analysis. Patients who achieved a continuing pregnancy that did not lead to term live birth were censored when they became pregnant. Cumulative term singleton live births were calculated by the same method.

To show that 1 year was sufficient for most patients to finish treatment, we calculated the proportion of term live births after four IVF cycles with mild treatment and three cycles with standard treatment. Couples who did not start a subsequent cycle within 6 months received a questionnaire to obtain all information about pregnancies that happened within 1 year after randomization. We analysed all cycles finished before 1 year after randomization—whether cancelled, pregnant, or non-pregnant.

We calculated costs for each cycle and also total costs per patient, accumulated over 1 year. Patients who withdrew before 1 year were assumed to have incurred no further costs related to treatment. Difference in mean total costs between the two treatments was calculated with a two-sample *t* test [158]. The difference in cumulative percentages was used to represent the difference in mean cost-effects (since pregnancy is a binary outcome). This trial is registered as an International Standard Randomized Clinical Trial, number ISRCTN74651862.

Role of the funding source

This study was funded by ZonMw (Netherlands), programme Doelmatigheidsonderzoek. This funding source had no role in study design, data collection, analysis, interpretation, or writing of the report. The first author had full access to all data and final responsibility for the decision to submit the paper for publication.

Results

404 patients were included in the study, and randomly assigned to either mild or standard treatment groups (Figure 5.1). The mild and standard groups did not differ from each other in terms of baseline clinical and demographic characteristics (Table 5.1). We did 769 IVF cycles in 1 year (444 in the 205 patients treated with a mild IVF strategy and 325 in the 199 patients treated with standard protocols). For mild treatment, the mean number of started cycles was 2.3 (SD 1.2); the mean for oocyte retrievals was 1.8 (1.1); and a mean of 1.5 (1.0) embryo transfers were done in 1 year. For standard treatment, these means were 1.7 (1.0), 1.6 (0.9), and 1.4 (0.9), respectively ($P < 0.0001$, 0.008, and

Table 5.1 Baseline demographics and clinical characteristics of patients assigned to mild or standard treatment

	Mild (*n* = 205)	Standard (*n* = 199)
Age woman (years)	32.9 (3.1)	32.8 (3.2)
Body-mass index (kg/m^2)	23.0 (2.6)	23.2 (2.5)
Duration of infertility (years)	3.6 (1.9)	3.6 (2.1)
Primary infertility	73.7%	72.9%
Child after previous IVF treatment	6.4%	5.6%
Cause of infertility		
Male	108 (53%)	113 (57%)
Tubal	31 (15%)	36 (18%)
Unexplained	55 (27%)	36 (18%)
Other	11 (5%)	15 (8%)

Values are mean (SD) or number (%) of patients.

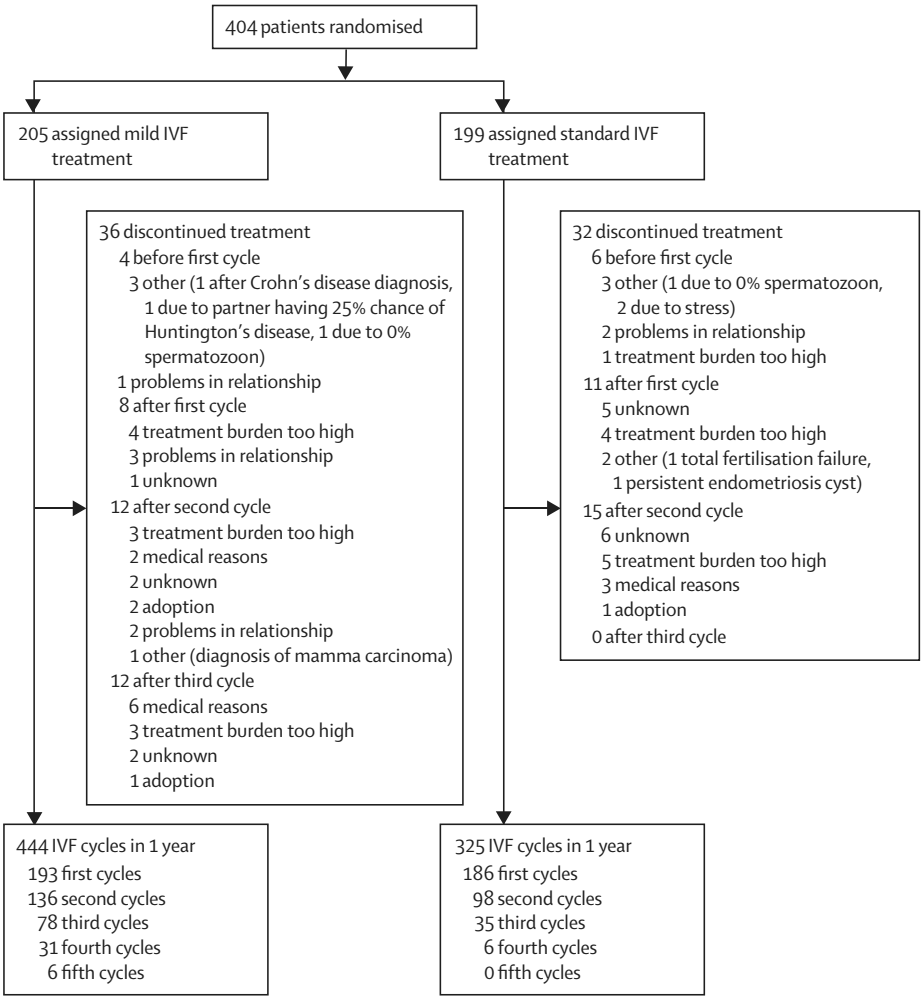
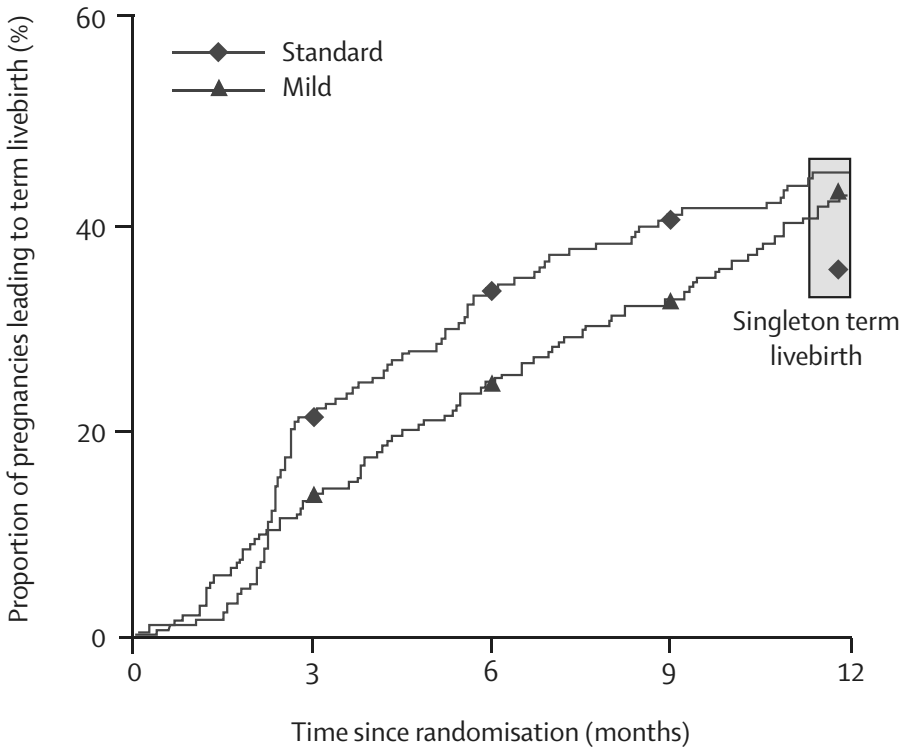


Figure 5.1 Trial profile

Note: Reason for withdrawals do not include pregnancy or preference for another stimulation protocol or embryo transfer policy.

0.5, respectively, by use of the *t* test). Table 5.2 shows cycle-specific characteristics of the IVF cycles finished within 1 year.

Of 96 continuing pregnancies (positive heartbeat on ultrasonography 10 weeks after embryo transfer) in the mild treatment group during the year-long study, 11 were spontaneous, 78 arose from fresh embryo transfer, six were from cryopreserved embryos, and one took place after so-called escape intrauterine insemination due to low ovarian response to stimulation. Of 102 continuing pregnancies in the standard treatment group, four were spontaneous, 93 happened after fresh embryo transfer, and five were from cryopreserved embryos. 86 term live births were produced in each of the two groups



Number of patients

Standard	199	152	123	106	97
Mild	205	174	149	130	109

Figure 5.2 Proportions of pregnancies leading to cumulative term livebirth within 12 months after starting IVF
Note:
Mild: mild ovarian stimulation with GnRH antagonist and single embryo transfer. Standard: standard ovarian stimulation with GnRH antagonist and dual embryo transfer. The shaded area represents the singleton livebirth rate after 12 months.

after 1 year of treatment. Figure 5.2 compares the 1-year cumulative proportion of pregnancies that produced term live births—43.4% with mild IVF treatment and 44.7% with the standard protocol. Standard IVF treatment resulted in 1.3% more term live births than mild treatment; the lower limit of the onesided 95% CI was −9.8%. The proportion of multiple pregnancies per couple during 1 year of IVF treatment was 0.5% (95% CI 0–2.7) with the mild strategy and 13.1% (8.7–18.6) with the standard strategy ($P < 0.0001$, χ^2 test). Table 5.3 shows the characteristics of children born from pregnancies within 12 months after randomization. The proportion of miscarriages was 15.0% with mild treatment and 17.1% with standard treatment.

Table 5.2 Cycle-specific characteristics of IVF cycles finished within 1 year

	Mild (*n* = 444)	Standard (*n* = 325)	*P*
Duration of ovarian stimulation (days)	8.3 (2.2)	11.5 (3)	< 0.0001*
Duration of injections (days)	8.5 (2.7)	25.3 (6.8)	< 0.0001*
Total dose of follicle stimulating hormone (IU)	1307 (529)	1832 (758)	< 0.0001*
Cancellation of started cycle	80 (18%)	27 (8.3%)	< 0.0001†
Number of oocytes per retrieval	6.9 (4.8)	8.5 (4.3)	< 0.0001*
‡ Number of embryos per retrieval	2.8 (2.7)	3.8 (2.9)	0.0002*
Number of cryopreserved embryos per fresh embryo transfer cycle	0.9 (1.8)	0.6 (1.4)	0.04*
Continuing pregnancy per started cycle (fresh embryos)	78 (17.6%)	93 (28.6%)	< 0.0001†
Continuing pregnancy per started cycle (cryopreserved embryos)	6 (1.4%)	4 (1.2%)	0.8†
Term livebirth per started cycle (fresh embryos)	70 (15.8%)	78 (24.0%)	0.003†
Term livebirth per started cycle (cryopreserved embryos)	49 (1.1%)	3 (0.9%)	0.8†
§ Ovarian hyperstimulation syndrome	6 (1.4%)	12 (3.7%)	0.04†

Values are mean (SD) or number (%) of cycles. *t-test for difference or †Pearson $\chi 2$ test for difference. ‡Embryos suitable for embryo transfer. § Mild, moderate and severe ovarian hyperstimulation syndrome.

Figure 5.2 shows that the cumulative proportion of pregnancies leading to singleton term live birth after 1 year was 43.4% in the mild group and 35.7% in the standard group.

36 and 32 patients withdrew from mild and standard treatment, respectively, for reasons shown in Figure 5.1. Although these patients withdrew at various stages during treatment, the study design allowed comparison of drop-out rates only for the first two treatment cycles. The drop-out rate for mild treatment was 5.1% after the first cycle and 11.2% after the second, compared with 9.1% and 19.5%, respectively, for standard treat-

Table 5.3 Pregnancy outcome following mild and standard IVF treatment

	Mild strategy		Standard strategy	
	Singleton	Multiple*	Singleton	Multiple
Livebirths (total)	91	1	76	26
Liveborn children	91	3	76	51†
Term livebirth (≥ 27 weeks' gestation)	86	0	69	17
Late preterm live birth (≥ 32-37 weeks' gestation)	2	0	6	6
Early preterm live birth (< 32 weeks' gestation)	3	1	1	3
Birth weight (kg)‡	3.34 (0.76)	1.34	3.35 (0.76)	2.34 (0.73)

*One set of triplets were born in the mild treatment group after intrauterine insemination in a cycle that was cancelled because of monofollicular growth. †One twin pregnancy resulted in one intrauterine death and one livebirth. ‡Birthweight is mean (SD). For multiple pregnancies the mean birthweight of the twins or triplets was used to calculate the overall mean birthweight per treatment group. The difference in distribution of term, late preterm, and early preterm livebirths between the standard and mild treatment group is significant (P = 0.04, χ^2 test with continuity correction).

ment. The drop-out rate per cycle was significantly lower in the mild treatment group than in the standard group (odds ratio = 0.53, 95% CI 0.28–0.98, $P = 0.04$, corrected for cycle number). Patients who withdrew were significantly younger than were those who finished treatment, with a mean age of 32.3 years (SD 3.4) and 33.3 years (3.2), respectively ($P = 0.047$). However, those who withdrew did not have significantly different durations of infertility ($P = 0.4$) or pregnancy histories ($P = 0.7$). Cycle cancellation or the number of oocytes retrieved did not significantly affect drop-out rates ($P = 0.4$ and $P = 0.6$, respectively, corrected for cycle number). 12 patients (6%) given mild treatment and 15 (8%) given standard treatment switched to another stimulation protocol or embryo-transfer strategy. When these patients were excluded from analysis, the 1-year cumulative proportion of pregnancies leading to term live birth was 43.2% in the mild group and 44.6% in the standard group.

The proportion of pregnancies leading to a term live birth was 50.3% after completion of three standard cycles and 52.4% after completion of four mild cycles. The difference, of 2.1% in favour of the mild strategy, has a lower one-sided 95% confidence bound of −6.6%.

Table 5.4 shows the lower total costs associated with mild treatment (difference € 2412, 95% CI 703–4131). Therefore, the incremental costs per additional pregnancy leading to term live birth with standard treatment, compared with mild treatment, would be € 185 000 (difference € 2412, success rate 0.447–0.434), with a lower 95% CI of € 22 000 (determined by 5000 bootstrap samples).

Figure 5.3 shows the distribution of unadjusted scores for four psychological variables during the first year after randomization for the mild and standard treatment groups. We found no difference in non-response to questionnaires between the two groups (47% for both, $P = 0.8$). Responders did not differ from the nonresponders in age ($P = 0.7$), duration of infertility ($P = 0.9$), or pregnancy history ($P = 0.07$). However, non-response

Table 5.4 Total costs (€) of IVF treatment over 12 months including costs of pregnancies up to 6 weeks after delivery (per couple)

	Mild ($n = 205$)	Standard ($n = 199$)	P*
IVF Treatment			
Technical Procedures	1083 (734)	991 (584)	0.16
Medication	1626 (1088)	1737 (1069)	0.3
Monitoring	750 (561)	576 (693)	0.006
Indirect costs	1948 (2280)	1740 (1845)	0.3
Pregnancy and neonatal period			
Medical costs	2547 (4553)	4899 (10 746)	0.01
Indirect costs	379 (1177)	802 (2270)	0.03
Total costs	8333 (5418)	10 745 (11 225)	0.006

Data are mean (SD). *Independent groups t-test (assuming unequal variances). Analysis includes costs of pregnancies up to 6 weeks after delivery. Mean costs for pregnancy are across the whole group, including those who did not achieve pregnancy.

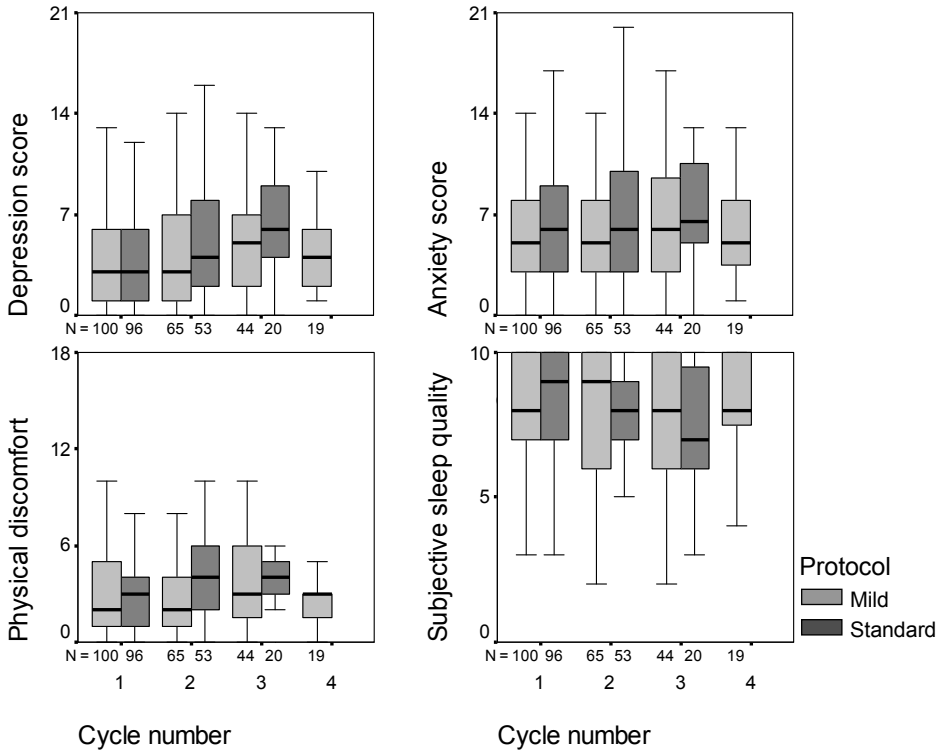


Figure 5.3 Distribution of unadjusted scores on psychological dimensions after IVF cycles in both mild and standard treatment groups
Note: High scores represent high anxiety, depression, and physical discomfort and better subjective sleep quality. Box shows IQR; whiskers show 95% CI; line in box shows median.

was associated with cycles in which no oocytes were retrieved or no embryo could be transferred ($P = 0.0002$, $P < 0.0001$, respectively). Non-response was not related to achievement of pregnancy ($P = 0.24$). In a multivariate analysis, only achievement of an embryo transfer remained statistically significant. Treatment strategy was not a significant factor in this analysis ($P = 0.6$). There were no significant differences between the two groups between the area under the curve for scores on the hospital anxiety and depression scale for anxiety ($P = 0.9$) or depression ($P = 0.8$), the Hopkins symptom checklist for physical discomfort ($P = 0.5$), and the subjective sleep quality scale ($P = 0.3$).

Discussion

Our study showed that, in women younger than 38 years, the 1-year cumulative proportion of pregnancies leading to term live births was much the same with a mild strategy for IVF, consisting of GnRH antagonist co-treatment with single embryo transfer, as with the standard IVF strategy. Moreover, overall discomfort to patients was similar, despite

an increase in the average number of IVF cycles for the group assigned mild treatment. The proportion of multiple pregnancies per couple was greatly reduced with the mild strategy, as were the overall costs per term live birth.

Previous studies that focused on outcomes in single cycles [66, 113, 156] have shown that single embryo transfer in women younger than 36 years is highly effective for reduction of multiple pregnancies, but at the expense of the probability of pregnancy per cycle. Although we also noted a reduced chance of term live births per cycle for the mild strategy, the cumulative 1-year proportion of pregnancies that produced term live births was about 45% for either strategy. Therefore, the reduced chances of birth per cycle with mild IVF treatment should be considered in the context of its shorter and less costly cycles of ovarian stimulation, less risk of ovarian hyperstimulation syndrome, reduced rates of discontinuation of treatment, and increased numbers of IVF cycles in a set time. The difference between the 1-year analysis and the per-treatment-group analysis was small, illustrating that 1 year was long enough for most couples to complete the treatment strategy (three standard cycles or four mild cycles).

For calculation of the chance of a term live birth per 12 months per couple, we counted every live birth as equivalent to one child—i.e., we did not count term-born twins as two live births. Term-born twins could be perceived as a positive outcome—e.g., for parents who wanted more than one child the need for subsequent IVF treatments might be reduced. However, in addition to the distinct increase in perinatal morbidity, mortality, and long-term health consequences associated with twin pregnancies, parents of multiple pregnancies have shown to be at greater risk of depression and anxiety [160]. Consideration of the benefits of single embryo transfer should also take account of the live births which might arise from the subsequent transfer of cryopreserved surplus embryos [66]. By contrast, others argue that only a singleton term live birth is a successful outcome of IVF [145].

We used the Kaplan-Meier method to calculate the 1-year cumulative proportion of term live births; this differs from standard method of censoring, which assumes that patients who drop out have a similar chance of pregnancy to patients who continue treatment [133]. Because we were able to use all information about pregnancies that happened within 1 year, we could do an intention-to-treat analysis of the true cumulative proportion of patients who achieved term live births, without making assumptions about pregnancy chance for those who withdrew (no censoring). The proportion of term live births we calculated is lower than those usually reported, since censoring masks the numbers of patients who discontinue treatment (e.g., because of discomfort). Censoring is therefore not appropriate for studies with endpoints linked to treatment-related stress.

Although the mild treatment group had more IVF cycles within 1 year, overall discomfort to patients in the two groups during that year was similar. We used assessments of discomfort at the end of each IVF cycle to calculate the cumulative discomfort score

over time. Although stress levels might have varied during and between treatment cycles, patients' discomfort associated with the mild strategy seemed to be stable over time, whereas the discomfort associated with standard treatment intensified during subsequent treatment cycles. The questionnaire response rate, of just 50%, was within normally reported ranges for this type of psychological assessment [161], and did not differ between the two treatment groups (data not shown). Women who had no oocyte retrieval or no embryo transfer were significantly less likely to respond than were other patients, which could have led these features to be underestimated in both treatment groups. However, this difference is unlikely to have biased the results in favour of either treatment strategy.

The potential health economic benefits of single embryo transfer have been investigated in only a few studies [128, 131]. One randomized trial suggested that a single embryo transfer strategy was associated with lower total costs per cycle than cycles in which two embryos were transferred, because of the associated reduction in multiple pregnancies [154]. Despite the higher average number of cycles that are possible in 1 year with the mild strategy (and consequently the higher monitoring and indirect costs) the overall costs per term live birth within that time were lower than those of the standard treatment strategy. Savings were mainly attributable to the reduction in multiple pregnancies. We assessed costs for a postnatal period of only 6 weeks after the expected date of delivery, which resulted in a conservative estimate of the additional costs, since prematurity is also associated with long-term health consequences [162].

Challenges to contemporary notions of success in assisted reproduction, which emphasise single cycle outcomes, could facilitate further development of IVF [117]. The Cochrane Menstrual Disorder and Subfertility group has proposed that success should be defined per IVF treatment period rather than per cycle [163]. The definition of success could be further refined to incorporate chances for term live birth (or healthy child) per IVF treatment period (which could include several cycles) in relation to cost, patients' discomfort, and risks of complications.

Our findings emphasise the medical, health, economic, and psychological benefits of mild IVF strategies in women younger than 38 years. However, if this mild IVF treatment strategy is to be widely implemented, IVF outcomes should be redefined in broader terms that encompass the interests of the couple, the child, and even the providers of health care. In other medical specialties, such as oncology, normal practice is to present success of a treatment strategy as survival per time period [164]. The chance that IVF can produce a healthy baby (or babies) needs to be weighed against the discomfort and risks of complications and costs associated with the treatment. Adoption of the endpoint of term delivery per time period (which might consist of several IVF cycles) would encourage patient-friendly stimulation protocols and single embryo transfer. In conclusion, our findings should encourage more widespread use of mild ovarian stimulation and single

embryo transfer in clinical practice. However, adoption of our mild IVF treatment strategy would need to be supported by counselling of both patients and health-care providers to redefine IVF success and explain the risks associated with multiple pregnancies [165] and by institution of reimbursement systems that encourage, rather than penalise, the practice of single embryo transfer [166].

Chapter 6

The psychological impact of IVF failure after two or more cycles of IVF with a mild versus standard treatment strategy

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Abstract

BACKGROUND: Failure of IVF treatment after a number of cycles can be devastating for couples. Although mild IVF strategies reduce the psychological burden of treatment, failure may cause feelings of regret that a more aggressive approach, including the transfer of 2 embryos, was not employed. In this study, the impact of treatment failure after two or more cycles on stress was studied, following treatment with a mild versus a standard treatment strategy.

METHODS: Randomized controlled two-centre trial (ISRCTN35766970). Women were randomized to undergo mild ovarian stimulation (including GnRH antagonist co-treatment) and single embryo transfer (n = 197) or standard GnRH agonist long-protocol ovarian stimulation with double embryo transfer (n = 194). Participants completed the Hospital Anxiety and Depression Scale prior to commencing treatment and 1 week after the outcome of their final treatment cycle was known. Data from women who underwent two or more IVF cycles were subject to analysis (n = 253).

RESULTS: Women who experienced treatment failure after standard IVF treatment presented more symptoms of depression 1 week after treatment termination compared with women who had undergone mild IVF: adjusted mean (± 95% confidence interval) = 10.2 (± 2.3) versus 5.4 (± 1.8), respectively, P = 0.01.

CONCLUSIONS: Failure of IVF treatment after a mild treatment strategy may result in fewer short-term symptoms of depression as compared to failure after a standard treatment strategy. These findings may further encourage the application of mild IVF treatment strategies in clinical practice.

Introduction

The implementation of IVF treatment strategies which combine shorter and milder ovarian stimulation protocols and single embryo transfer (SET) can reduce short-term side effects related to ovarian stimulation [161] and prevent multiple pregnancies [167]. A possible drawback of milder strategies is the higher cycle cancellation rate and the necessity of a greater number of treatment cycles to achieve pregnancy [64]. Women who undergo this type of IVF treatment may therefore have to face the uncertainty and disappointment related to a failed IVF cycle more frequently. This could in turn result in an increase in treatment related stress. However, we have recently shown that the combination of SET with mild ovarian stimulation in IVF results in similar overall patient discomfort over 1 year of treatment compared with standard stimulation with the transfer of two embryos [167]. Furthermore, Højgaard *et al.* [68] suggest that treatment burden increases over cycles more in women treated by a standard long protocol compared with women receiving mild stimulation. However, it remains unclear whether the psychological consequences of treatment failure after multiple cycles of mild IVF are more or less severe than failure of standard IVF regimens.

In general, IVF treatment failure seems to be associated with a deterioration of emotional well being [31]. In a study by Verhaak *et al.* [41], over 20% of the women who did not achieve pregnancy showed subclinical depression and/or anxiety up to 6 months after treatment termination. It may be postulated that women who receive milder approaches in IVF are more prone to regret the choice for a new and mild treatment compared with women receiving the standard IVF protocol when facing overall treatment failure and confronting the reality of childlessness. On the other hand, reduced stress and discomfort during milder IVF treatment may have a positive impact on the psychological status afterwards, even when pregnancy was not achieved.

In the present study, self-reported symptoms of depression and anxiety 1 week after treatment termination in women receiving mild ovarian stimulation using GnRH antagonist co-treatment combined with SET were compared with women receiving standard IVF treatment (GnRH agonist long protocol with the transfer of two embryos). The principal focus of the study was the impact of unsuccessful IVF treatment on women's psychological well being following the mild versus standard strategy.

Materials and methods

Subjects

Couples with an indication for IVF or IVF/ ICSI were recruited at the Erasmus MC University Medical Centre, Rotterdam (The Netherlands) and the University Medical Centre,

Utrecht (The Netherlands), between February 2002 and February 2004. Only couples with no previous unsuccessful IVF treatment were included. The study was limited to women aged < 38, with a regular menstrual cycle (25–35 days) and a body mass index of 18–28 kg/m^2. These study criteria were chosen to exclude women for whom either mild stimulation or SET would not normally be considered suitable. Only women who had sufficient knowledge of the Dutch language to fill out the questionnaires were invited to take part in the psychological study.

Intervention

Standard stimulation with the transfer of two embryos

In the standard treatment arm, a GnRH agonist (leuproline 0.2 mg/day; or triptoreline 0.1 mg/day) was started in the midluteal phase of the preceding cycle. After ~2 weeks of GnRH agonist administration subcutaneously (s.c.), ovarian stimulation was started with recombinant follicle-stimulating hormone (recFSH) s.c. at a daily dose of 150 IU/day. When the leading follicle had reached at least 18 mm in diameter and at least one additional follicle measured > 15 mm, human chorionic gonadotrophin (hCG) 10 000 IU s.c. was administered to induce final oocyte maturation. Oocyte retrieval and fertilization *in vitro* was performed according to standard procedures as described previously [118]. A maximum of two embryos were transferred. Good quality embryos were cryopreserved and thawed for transfer in a subsequent unstimulated cycle. Luteal phase supplementation with progesterone, 600 mg/day, intravaginally was started on the evening of the oocyte retrieval and continued for 12 days.

Mild stimulation with SET

In the mild strategy group, ovarian stimulation was performed with a fixed starting dose of 150 IU recFSH s.c. per day, initiated on the fifth cycle day. GnRH antagonist s.c. (ganirelix, 0.25 mg/day; or cetrorelix, 0.25 mg/day) was commenced when at least one follicle ≥ 14 mm was observed [110]. Similar criteria applied for hCG, oocyte retrieval, fertilization and luteal phase support procedures as in the standard IVF group. Only the best quality embryo was transferred. Good quality embryos were cryopreserved for transfer in subsequent cycles.

Measures

Demographic data (e.g. age) and information on the couple's infertility history (e.g. duration of infertility) were obtained from medical records and patient questionnaires. The Hospital Anxiety and Depression Scale (HADS) was used to measure anxiety and depression experienced by subjects in the week prior to screening [102]. Both subscales (range 0–21) of the HADS consist of seven items, which are scored on a 4-point-Likert

scale from 0 to 3. Higher scores indicate the presence of more symptoms. Cut-off scores for *possible* and *probable* depressive and anxiety disorder are 7/8 and 10/11, respectively. The Dutch version of the HADS has demonstrated good test-retest reliability, homogeneity and internal consistency [103].

Study design

This psychological study was part of a two-arm randomized controlled, non-inferiority, effectiveness trial, which encompasses the medical, economical and psychological evaluation of mild ovarian stimulation combined with SET. Sample size was determined by a power calculation of the number required to demonstrate non-inferiority of the mild strategy in achieving a live birth within 12 months of commencing treatment [158]. Couples were randomized into either the mild treatment group (GnRH antagonist co-treatment combined with SET) (n = 205) or the standard treatment group (standard ovarian stimulation including a GnRH agonist long-protocol combined with the transfer of two embryos) (n = 199). Block-randomization, stratified by clinic, was applied to achieve balance between the two groups within each hospital. The study design has recently been described in detail [158] and the clinical outcomes of this randomized controlled trial (RCT) have recently been published elsewhere [167]. Only women who had sufficient knowledge of the Dutch language to fill out the questionnaires were invited to take part in the psychological study (n = 391). Psychological outcomes during the first cycle have recently been published [161]. The analyses in the present article were limited to the subgroup of patients that received two or more IVF cycles (n = 253). Women were asked to complete the HADS prior to commencing IVF treatment and one week after treatment outcome of every IVF cycle, with the exception of the first cycle.

Procedure

The study was approved by the Ethical Review Boards of the two participating clinics. Patients who met the eligibility criteria were either recruited by their treating physician during the IVF planning consultation (Rotterdam) or by one of the medical researchers before their IVF planning consultation (Utrecht). Randomization was carried out using sealed envelopes. Envelopes were opened by the physician/researcher after written consent was obtained from both partners. Women received a booklet containing the baseline questionnaire. Subsequent questionnaires were sent by mail. Couples in the mild IVF group were offered an extra fourth reimbursed treatment cycle to compensate for the possible reduction in birth rate.

Statistical analyses

Demographical data were analysed using Student's t-test for continuous variables and χ^2-test for categorical variables. Psychological assessments from the final stimulated IVF

treatment cycle were used for analysis. Multivariate analysis of covariance was performed on depression and anxiety scores with *treatment strategy* as independent variable and *pregnancy status* as effect modifier, while controlling for baseline depression and anxiety scores. *Pregnancy status* was defined as being either *not pregnant and no remaining cryopreserved embryos*, *not pregnant but with remaining cryopreserved embryos* or *pregnant*. χ^2 analysis was used to compare the percentage of women who had HADS scores above the cut-off between the mild and standard IVF group. All analyses were performed using the Statistical Package for the Social Sciences (SPSS version 10.1). Significance testing on all outcome measures was done at 0.05 level of significance (two-tailed).

Results

Of the 391 women that were recruited, 32 women did not receive their allocated intervention. Of the remaining group, 253 women received multiple IVF cycles (Figure 6.1). No significant differences between the mild and standard IVF groups were found for age, duration of infertility, type of infertility (primary or secondary), cause of infertility and baseline psychological scores (Table 6.1). Women in the mild strategy arm received more IVF cycles than the standard strategy group (mean = 3.45; range = 2–6 versus mean = 2.88; range = 2–5). One hundred and thirty-seven women failed to provide endpoint psychological measurements. These were considered as study drop-outs. They differed from participants in pregnancy status only, and no differences between drop-outs and participants were observed for baseline stress variables (Table 6.2). Twelve further women were dropped from the analysis, since they had missing data for either baseline psychological variables or pregnancy status.

The adjusted means and 95% confidence intervals of the HADS scores are depicted in Table 6.3. Multivariate analysis of covariance showed no main effects of *treatment strategy*. Overall, women in the mild IVF strategy arm did not differ from women in the standard strategy arm on psychological variables. However, a modification effect of *treatment strategy by pregnancy status* was found for depression (P = 0.002). In the group of women who did not get pregnant and had no cryopreserved embryos, those who underwent standard IVF showed more depressive symptoms than those who underwent mild IVF (P = 0.007). The modification effect of *treatment strategy by pregnancy status* for anxiety was not significant, but a trend was found (P = 0.07). Again, in women who did not get pregnant without cryopreserved embryos, the standard IVF group demonstrated more symptoms of anxiety than the mild IVF group (P = 0.04).

Additionally, significant main effects of *pregnancy status* were found for depression (P < 0.001) and anxiety (P = 0.01). Pregnant women showed fewer symptoms of depression and anxiety than non-pregnant women. Also, the main effects of both baseline depres-

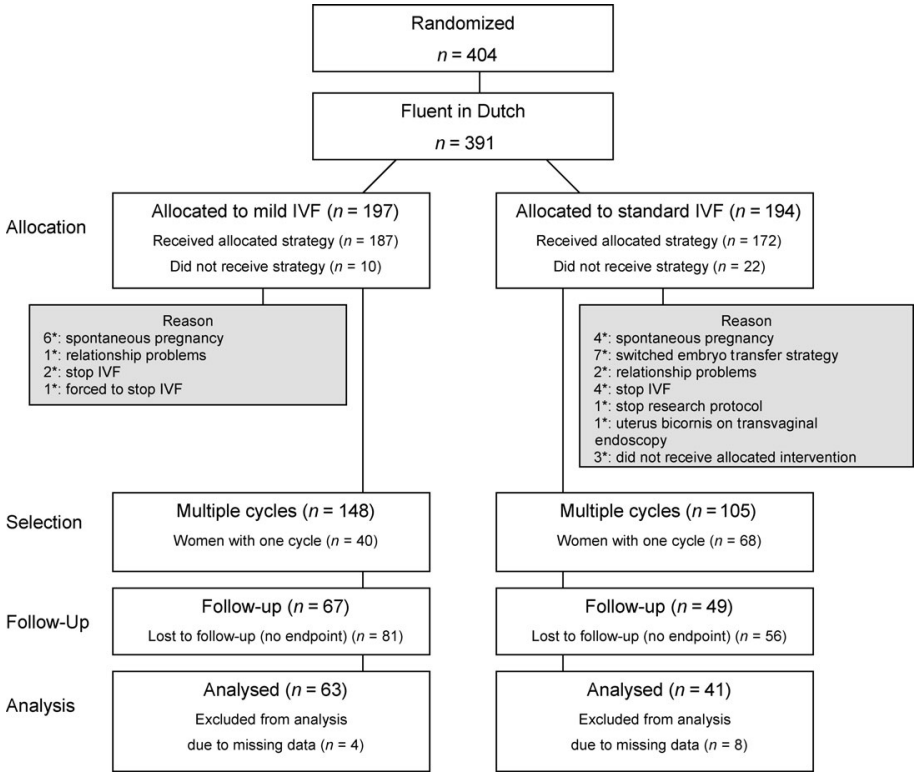

Figure 6.1 CONSORT statement flow diagram

Table 6.1 Baseline characteristics of treatment strategy groups

Variable	Mild strategy (*n* = 148)	Standard strategy (*n* = 105)
Age (years), mean (SD)	33.0 (3.0)	32.8 (3.3)
Duration of infertility (years), mean (SD)	3.7 (1.9)	3.6 (2.2)
Type of infertility		
Primary	108	75
Secondary	40	30
Cause of infertility		
Female	26	22
Male	80	60
Both	42	23
Baseline HADS-Depression (SD) (*n*)	2.6 (2.6) (134)	2.5 (2.5) (93)
Baseline HADS-Anxiety (SD) (*n*)	5.0 (3.7) (134)	4.7 (3.2) (93)

Table 6.2 Baseline characteristics of participants versus drop-outs

Variable	Participants (n = 116)	Drop-outs (n = 137)
Age (years), mean (SD)	33.0 (3.4)	32.9 (2.9)
Duration of infertility (years), mean (SD)	3.6 (2.0)	3.6 (2.1)
Type of infertility		
Primary	85	98
Secondary	31	39
Cause of infertility		
Female	17	31
Male	68	72
Both	31	34
Treatment strategy		
Standard	49	56
Mild	67	81
Pregnancy status after final treatment cycle		
Not pregnant	47	73[a]
Pregnant	69	64
Baseline HADS-Depression (SD) (n)	2.7 (2.8) (108)	2.5 (2.3) (119)
Baseline HADS-Anxiety (SD) (n)	4.8 (3.7) (108)	4.9 (3.5) (119)

[a] $P = 0.05$, two-tailed.

Table 6.3 Adjusted means and 95% confidence intervals for depression and anxiety (HADS) during the last stimulated IVF cycle for women with multiple IVF cycles[a]

	Depression Mean (95% CI)	Anxiety Mean (95% CI)	n
Not pregnant, no cryopreserved embryos			
Mild strategy	5.4 (±1.8)	6.0 (±1.8)	17
Standard strategy	10.2 (±2.3)	10.2 (±2.4)	10
Not pregnant, with cryopreserved embryos			
Mild strategy	8.3 (±3.6)	8.0 (±3.7)	4
Standard strategy	4.4 (±2.6)	7.2 (±2.7)	8
Pregnant			
Mild strategy	3.4 (±1.1)	5.4 (±1.1)	42
Standard strategy	3.4 (±1.5)	5.8 (±1.5)	23

[a] Multivariate analysis of covariance.

Table 6.4 Percentages of women with clinically relevant depression (HADS-D) and anxiety (HADS-A) scores after multiple IVF cycles

	Treatment strategy	
	Mild[a]	Standard
Possible depression disorder, HADS-D > 7	19.4 (13/67)[b]	38.8 (19/49)[b]
Probable depression disorder, HADS-D > 10	11.9 (8/67)	8.2 (4/49)
Possible anxiety disorder, HADS-A > 7	31.3 (21/67)	40.8 (20/49)
Probable anxiety disorder, HADS-A > 10	14.9 (10/67)	26.5 (13/49)

[a] χ^2-analysis.

[b] $P < 0.05$, two-tailed.

sion ($P < 0.001$) and baseline anxiety ($P < 0.001$) were significant, as well as the interaction term *baseline anxiety by treatment strategy* ($P = 0.02$). Higher baseline depression scores were associated with higher endpoint depression scores, whereas higher baseline anxiety scores were associated with higher endpoint anxiety scores, especially in women undergoing standard IVF. When the number of IVF cycles was taken into account as a confounder in the analysis, no association was found with psychological scores (HADS-D: $P = 0.31$; HADS-A: $P = 0.21$). Therefore, this factor was omitted from the final model.

Percentages of women who showed clinically relevant depression and anxiety scores one week after the outcome of their final IVF cycle are depicted in Table 6.4. Chi²-analyses showed that 38.8% (19/49) of the women in the standard IVF group who underwent multiple IVF cycles scored above the cut-off score for *possible* depressive disorder against 19.4% (13/67) of the women in the mild IVF group ($P = 0.04$). No significant differences were found for *probable* depressive disorder and anxiety between mild and standard IVF arms.

Discussion

The main finding of this study is that a mild IVF treatment strategy is associated with fewer symptoms of depression after overall treatment failure than standard IVF treatment. One week after they had finished their last treatment cycle, non-pregnant women without remaining cryopreserved embryos who had been repeatedly treated by a mild protocol reported significantly fewer symptoms of depression than non-pregnant women without remaining cryopreserved embryos who had received the standard IVF strategy. Furthermore, women who underwent multiple cycles of standard IVF showed more often clinically relevant symptoms of depression after treatment failure as compared to women who underwent multiple cycles of mild IVF.

Previous analyses of this RCT showed that a mild IVF treatment strategy results in similar patient discomfort during a first cycle as standard treatment [161]. However, the results presented in this article suggest that treatment burden becomes more severe with every cycle in women treated by a standard long protocol as compared to women who received mild IVF treatment. These findings are consistent with a previous study [68]. A possible explanation could be that prolonged ovarian suppression with the use of GnRH agonists caused more symptoms of depression in women who received standard IVF. Women who receive GnRH agonist medication experience a loss of endogenous ovarian gonadotrophin stimulation, which results in a decrease in both estrogens and androgens [168]. Results of a study by Warnock *et al.* [168, 169] suggest that depressive symptoms increase in women on GnRH agonist therapy for endometriosis and are temporally related to the time women were taking the GnRH agonists. Case reports show that symptoms

related to GnRH therapy usually remit 4–6 weeks after the last injection [170]. No significant differences in depression and anxiety between groups were found in women who achieved pregnancy.

The results of this study also suggest that women who were treated by a mild IVF strategy did not regret their decision to take part in this study, even after overall treatment failure. The fact that only a small percentage of couples in the mild stimulation group indicated any wish to change to the standard treatment protocol after one or more failed cycles [167] supports this interpretation. Although psychological scores were in the normal range for the mild strategy group, this does not imply that doubts about this strategy were non-existent. Even though mild ovarian stimulation with SET can result in similar cumulative term live birth rates in one year of treatment compared to standard stimulation with the transfer of two embryos [167], patients might still prefer the lower frequency of treatment cycles associated with standard IVF protocols. It was shown previously that the possible lower pregnancy chance *per transfer* is the most important motive for patients to decide to transfer two embryos instead of one [171]. Therefore, counselling should not only entail the medical aspects of IVF treatment, but also the psychological consequences that can differ between different treatment strategies as the present study has shown. Furthermore, counselling should be a continuing process, since treatment implications seem to vary during different treatment stages.

Besides the strengths of this study (e.g. RCT, large sample, validated questionnaire), it also suffers from limitations. No questionnaire was completed after the first cycle, since this was considered to be an excessive burden to the patient who had to keep a daily diary throughout the first cycle [161]. Therefore, it is unknown how women who received only one cycle felt after treatment termination. Another limitation of the current study is the short length of the follow-up period (e.g. one week). To determine the long-term psychological consequences of mild IVF, a longer follow-up period is needed. An ongoing negative psychological impact of unsuccessful infertility treatment has been reported up to six months after treatment termination [41].

No records were kept on non-respondents and therefore the general applicability of the study results is unclear. On the basis of the average number of couples which yearly undergo IVF treatment in the two participating hospitals and who would qualify for the study (n = 300), the estimated response rate was ~65% (391/600) [161]. Furthermore, this study suffered from a high drop-out rate (~54% (137/253)). This might have introduced a reporting bias, since one could hypothesize that women who experienced more symptoms were less likely to fill in questionnaires. However, no differences in baseline anxiety and depression scores were found between study drop-outs and women who did complete the study. High attrition rates are not uncommon in this research area: in a similar longitudinal study by Verhaak *et al.* [41] the attrition rate was ~45%. Tracking couples throughout their IVF treatment provides a practical challenge.

In conclusion, the results of this study provide the first evidence that the use of a mild IVF treatment strategy which combines GnRH antagonist ovarian stimulation and SET is associated with less patient stress immediately following overall treatment failure than standard IVF treatment. The acceptability of mild IVF protocols by patients and clinicians might be facilitated by these results. Couples facing IVF need to be thoroughly counselled about the medical, psychological and economical implications of their choice of treatment strategy in order to maximize patient autonomy.

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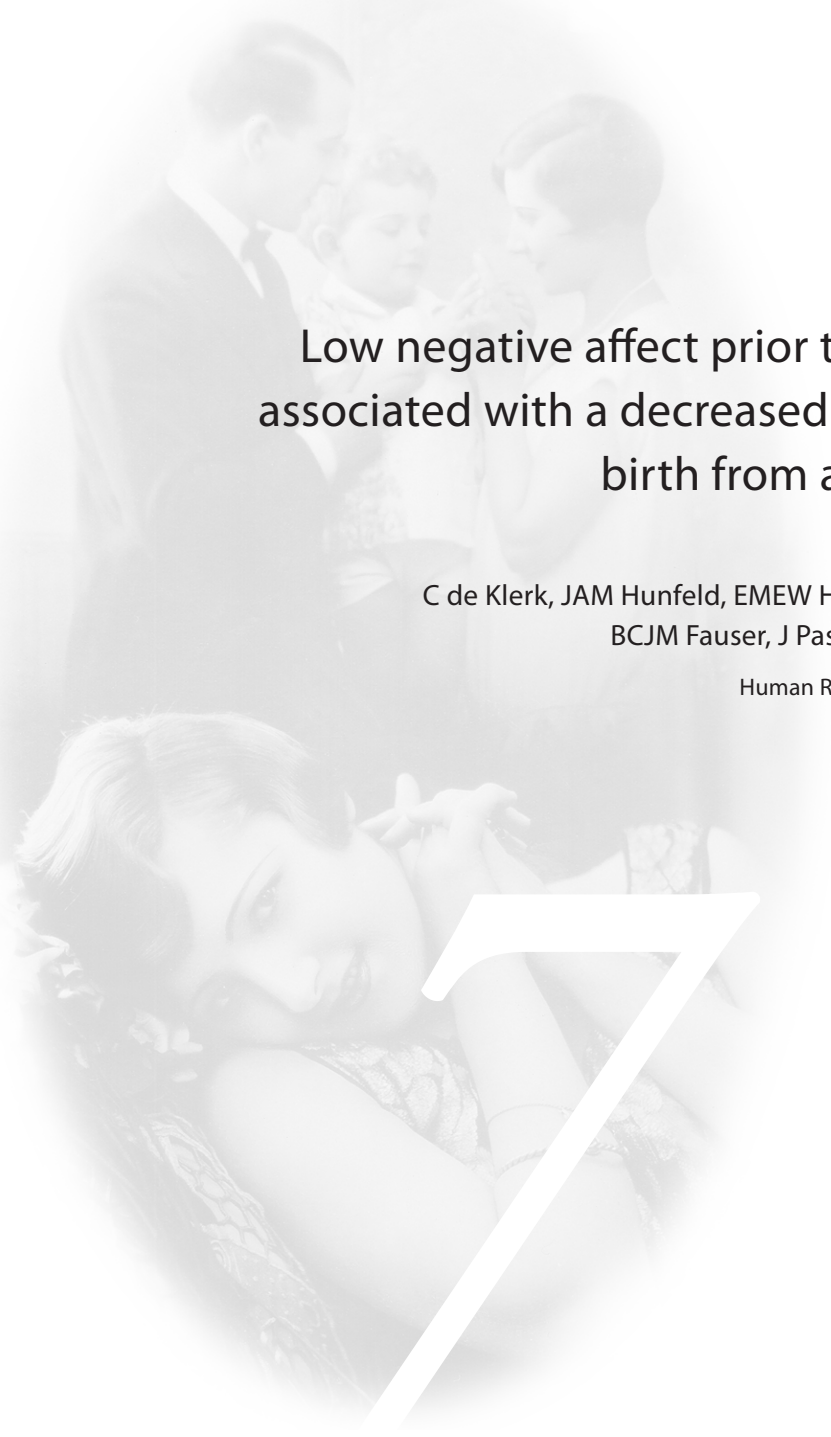

Chapter 7

Low negative affect prior to treatment is associated with a decreased chance of live birth from a first IVF cycle

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Abstract

BACKGROUND: Psychological variables, such as anxiety and depression, may have a negative impact on IVF outcomes, but the evidence remains inconclusive. Previous studies have usually measured a single psychological parameter with clinical pregnancy as the outcome. The objective of the current study was to determine whether pretreatment or procedural psychological variables in women undergoing a first IVF cycle affect the chance of achieving a live birth from that cycle.

METHODS: Between February 2002 and February 2004, 391 women with an indication for IVF were recruited at two University Medical Centres in the Netherlands. Pretreatment anxiety and depression were measured with the Hospital Anxiety and Depression Scale. The Daily Record Keeping Chart was used to measure negative and positive affect before treatment and daily during ovarian stimulation. Multiple stepwise forward logistic regression analysis was performed with term live birth as the dependent variable.

RESULTS: Regression analysis showed that women who expressed less negative affect at baseline were less likely to achieve live birth ($P = 0.03$). After one IVF cycle, women who received a standard IVF strategy were more likely to reach live birth delivery than women who received a mild IVF strategy ($P = 0.002$). A male/female indication for IVF was associated with a higher chance of achieving term live birth than a female only indication ($P = 0.03$). Age, duration of infertility or type of infertility were not independent predictors of live birth.

CONCLUSIONS: The relationship between psychological parameters and IVF success rates is more complex than commonly believed. The expression of negative emotions before starting IVF might not be always detrimental for outcomes.

Introduction

IVF is a demanding and stressful treatment for patients, requiring daily hormone injections, ultrasound scans, semen analysis and invasive procedures, such as oocyte retrieval [91]. Furthermore, IVF is usually the final treatment option for infertile couples, and failure will probably mean they will remain childless. It is therefore not surprising that both women and men demonstrate elevated levels of anxiety during IVF treatment, especially at oocyte retrieval and pregnancy testing [93, 161]. In women who do not achieve pregnancy via IVF, an increased prevalence of subclinical anxiety and depression has been reported [41].

Although IVF treatment is known to increase stress [43], the evidence for an association between stress and IVF outcome is inconclusive [17, 172, 173]. Several studies have shown psychological stress to have a negative impact on IVF treatment outcomes. Smeenk and colleagues [83] e.g. found that pre-existing psychological variables, especially state anxiety, are independently related to the probability of becoming pregnant after IVF/ICSI. In contrast, a recent large multi-centre study showed no associations between stress levels and IVF outcomes [87]. In the latter study, depression and anxiety were measured prior to the first cycle of IVF, and again one day before oocyte retrieval.

The conflicting results in this research area may reflect limitations in study sample size and design, since most previous studies were either retrospective or cross-sectional. Moreover, psychological measurements have usually been limited to a single stress parameter. Since the majority of studies reported clinical pregnancy as the endpoint, data relating to spontaneous abortion and premature delivery are scarce. To date, only one study has reported live birth delivery as an endpoint [84]. In this study, live birth rate was negatively influenced by baseline stress, but not by procedural stress. If the impact of stress on IVF outcomes is to be properly addressed, more large prospective studies that apply multiple stress measures and report live birth as the endpoint are required. The objective of the present two-centre study was therefore, to prospectively examine anxiety, depression and affect in women before and during a first IVF or IVF/ICSI cycle and to study their relationship with live birth delivery rates.

Materials and methods

Subjects

Between February 2002 and February 2004, couples about to start their first cycle of IVF or IVF/ ICSI treatment at the Erasmus MC University Medical Centre, Rotterdam, and the University Medical Centre, Utrecht, were recruited to the study. The study was approved by the Ethical Review Boards of the two participating clinics. Only couples with no previ-

ous unsuccessful IVF treatment were included. Inclusion criteria limited participation to women aged < 38 yrs, with a regular menstrual cycle (25–35 days) and a body mass index of 18–28 kg/m^2. These study criteria were chosen to exclude women for whom either mild stimulation or single embryo transfer (SET) was considered *a priori* to be inappropriate [110]. Couples received either mild ovarian stimulation (including GnRH antagonist co-treatment) and SET or conventional GnRH agonist long-protocol ovarian stimulation with the transfer of two embryos [158, 167]. Patients who met the eligibility criteria were either recruited by their treating physician during the IVF planning consultation (Rotterdam) or by one of the medical researchers before their IVF planning consultation (Utrecht). After written consent was obtained from both partners, women received a booklet containing all psychological questionnaires.

Measures

The Hospital Anxiety and Depression Scale (HADS) is a general stress measure that was developed as a screening tool to measure anxiety and depression experienced by medical patients in the past week [102]. Both subscales (range 0–21) of the HADS consist of seven items, which are scored on a 4-point-Likert scale from 0–3. Higher scores imply the presence of more symptoms. Cut-off scores for possible and probable depressive and anxiety disorder are 7/8 and 10/11, respectively. The Dutch version of the HADS has shown good test-retest reliability, homogeneity and internal consistency [103].

The 21 items of the Daily Record Keeping Chart (DRK) represent emotional reactions common to women receiving infertility treatment [93, 101]. Each item is rated on a 4-point-Likert scale ('none' to 'severe'). Scores on four subscales can be obtained: depression/anger; uncertainty; anxiety; and positive affect (range 0–12). The depression/anger, uncertainty and anxiety subscales can be combined into a single scale measuring negative affect (range 0–36). The DRK has demonstrated good criterion-related validity, good convergent validity and good internal consistency. Cronbach coefficient alphas varied from 0.76 to 0.88 for the individual subscales [101]. The DRK is available in Dutch translation [150].

Additional data on the subjects' demographics and infertility history were obtained from medical records.

Study design

This psychological study was part of a two-arm randomized controlled, non-inferiority, effectiveness trial, which encompassed the medical, economical and psychological evaluation of mild ovarian stimulation combined with SET compared with standard IVF treatment. Clinical outcomes of this randomized controlled trial have recently been published elsewhere [167]. Only women who had sufficient knowledge of the Dutch language to fill out the questionnaires were invited to take part in the psychological study (n = 391).

Pretreatment stress was measured with the HADS on the day of IVF planning consultation carried out within 6 weeks of commencing treatment. Women also completed the DRK daily for 1 week, starting on the day of the planning consultation. Procedural stress was measured daily with the DRK from the first day of ovarian stimulation until the day before oocyte retrieval. The endpoint chosen for this study was term (≥ 37 weeks gestation) live birth resulting from the first cycle of IVF.

Statistical analyses

Demographics and data on infertility history were analysed using Student's *t*-test for continuous variables and χ^2-test for categorical variables. Daily DRK scores were computed into two average scores: one for baseline and one for ovarian stimulation. Group differences in psychological variables between women who achieved live birth and women who did not were analysed using Student's *t*-test. Multiple stepwise forward logistic regression analysis was performed with term live birth as the dependent variable. Independent variables included all psychological variables, age, duration of infertility, cause of infertility, type of infertility and IVF strategy. All analyses were performed using the Statistical Package for the Social Sciences (SPSS version 10.1). Significance testing on all outcome measures was done at 0.05 level of significance (two-tailed).

Results

Of the 391 women that were recruited, 32 (8%) women dropped out of the study before commencing a first IVF cycle. Ten women had a spontaneous pregnancy, ten women did not start IVF treatment, and twelve women discontinued participation in the study [167]. Seventy women (19%) failed to fill out one or more baseline psychological questionnaires and were therefore excluded from analysis. The excluded women differed significantly from analysed women only in terms of cause of infertility (Table 7.1). Of the remaining 289 women, seventy-three participants (25%) achieved a live term delivery after the first IVF cycle. Table 7.2 shows the sample characteristics with respect to psychological variables of women who achieved and failed to achieve live birth. Univariate testing showed that the mean score for baseline negative affect was significantly lower in the latter group ($P = 0.02$). With regard to changes in affect between baseline and ovarian stimulation, no significant differences were found between these groups. Pearson correlation coefficients between psychological variables are shown in Table 7.3.

The findings of the stepwise logistic regression analysis are given in Table 7.4. Live birth was predicted positively by baseline negative affect as measured with the DRK ($P = 0.03$). Baseline anxiety, depression and positive affect as well as affect (both positive and negative) during ovarian stimulation were omitted from the model due to a lack of

Table 7.1 Baseline demographical and medical characteristics of participants

Variable	Analysed women (n = 289)	Non-analysed women (n = 70)
Age (years), mean (SD)	32.8 (3.1)	32.8 (2.9)
Duration of infertility (years), mean (SD)	3.6 (1.9)	3.6 (2.3)
Type of infertility		
Primary	222 (76.8%)	46 (65.7%)
Secondary	67 (23.2%)	24 (34.3%)
Cause of infertility		
Female	46 (15.9%)	22 (31.4%)[a]
Male	161 (55.7%)	33 (47.1%)
Female/male	82 (28.4%)	15 (21.4%)
IVF strategy		
Standard	137 (47.4%)	35 (50%)
Mild	152 (52.6%)	35 (50%)
IVF outcome		
No term live birth	216 (75.7%)	52 (74.3%)
Term live birth	73 (25.3%)	18 (25.7%)

[a] $P < 0.05$, two-tailed.

Table 7.2 Psychological characteristics of participants

Variable mean (SD)	Women who achieved live birth (n = 73)	Women who failed to achieve live birth (n = 216)
Baseline anxiety	5.1 (3.9)	5.0 (3.4)
Baseline depression	2.5 (2.8)	2.6 (2.6)
Baseline positive affect	7.5 (2.6)	7.8 (3.2)
Baseline negative affect	6.4 (4.7)	5.0 (4.5)[a]
Positive affect during ovarian stimulation	6.9 (2.9)	7.2 (3.2)
Negative affect during ovarian stimulation	7.2 (6.1)	6.7 (5.4)

[a] $P < 0.05$, two-tailed.

Table 7.3 Pearson correlations between psychological variables

	1	2	3	4	5	6
1. Baseline anxiety	-	.60[a]	-.39[a]	.53[a]	-.31[a]	.41[a]
2. Baseline depression		-	-.43[a]	.45[a]	-.37[a]	.33[a]
3. Baseline positive affect			-	-.46[a]	.79[a]	-.27[a]
4. Baseline negative affect				-	-.31[a]	.55[a]
5. Treatment positive affect					-	-.47[a]
6. Treatment negative affect						-

[a] $P < 0.01$, two-tailed.

Table 7.4 Logistic regression model with variables predicting term live birth[a]

Variable	OR	*P*-value	95% CI
Baseline negative affect			
Continuous	1.07	0.03	[1.01, 1.1]
IVF strategy			
Standard[b]	1.0		
Mild	0.38	0.002	[0.21, 0.69]
Cause of infertility			
Female factor[b]	1.0		
Male factor	1.74	0.27	[0.66, 4.58]
Male/female factor	3.53	0.03	[1.27, 9.79]

[a] Optimism corrected value by bootstrapping = 0.62 [182].

[b] Reference category.

OR: odds ratio; CI: confidence interval.

correlation with live birth. Of the medical variables, IVF strategy (mild or standard) and cause of infertility were shown to have a significant effect on the probability of live birth delivery. After one IVF cycle, women who had received a standard IVF strategy were more likely to reach live birth delivery than women who underwent a mild IVF strategy ($P = 0.002$). Furthermore, a male/female indication for IVF was associated with a higher chance of achieving term live birth than a female only indication for IVF ($P = 0.03$). In this study neither age, duration of infertility or type of infertility were found to be independent predictors of live birth.

Discussion

This study examined the relationship between pretreatment and procedural psychological variables with term live birth in women undergoing a first IVF or IVF/ICSI cycle. No evidence was found for an association between psychological variables and IVF outcome when using a general depression and anxiety measure. However, a small but significant effect of DRK-scores on live birth rates was observed. Perhaps surprisingly, women who showed few feelings of anger, depression, uncertainty and/or anxiety (e.g. negative affect) before treatment were less likely to achieve term live birth than women who expressed a moderate level of negative affect. Neither positive affect nor negative affect during ovarian stimulation did influence the possibility of live birth.

Infertility-specific questionnaires such as the DRK are likely to be more sensitive to the diverse reactions women might experience during the various stages of IVF treatment than general stress measures such as the HADS. The fact that the DRK is a prospective diary-based measure, whereas the HADS is a retrospective measure, may further benefit the sensitivity of the DRK. This might be a reason why the results from this study are incongruent with earlier studies [83] in which general stress measures were mostly used.

The results of a recent study by Cooper *et al.* [174], in which an infertility-specific questionnaire (e.g. Fertility Problem Inventory) was used, were in line with the results of the present study. The authors reported that couples who did not get pregnant during their first IVF cycle expressed less infertility-related stress before treatment than conceiving couples. However, no conclusions can be made about the effect of strong infertility-related stress and IVF outcomes based on the results of either study, as mean scores on the infertility-related stress questionnaires were all in the low to moderate range. Therefore, it remains possible that the expression of high infertility-related stress is harmful. However, the expression of moderate infertility-related stress seems more beneficial than extreme low levels of negative affect.

It may be hypothesized that the association between extreme low levels of negative affect and negative IVF outcomes could be explained by the fact that women receiving IVF frequently use defence mechanisms such as repression and denial to cope with the emotional strain associated with treatment. Previous studies have shown that patients underreport feelings of stress during IVF treatment, afraid that they might be dropped from the IVF programme or that they might be "jinxed" [93, 175]. Positive thinking seems to be the most frequently used coping strategy during IVF treatment [176]. In the present study, low scores for negative affect might indicate the use of repression and positive thinking strategies. It is possible that the use of these strategies elicit physiological responses that adversely affect IVF outcomes. Psychological defence strategies, such as repression, have been found to be associated with autonomic reactivity that may be a risk factor for medical illness [177]. Future studies are needed to explore the possible association between repressive coping strategies and IVF outcomes.

In contrast to previous studies [178, 179] no associations between age, duration of infertility, and live birth rates were found in the current study, possibly due to the study's strict inclusion criteria. However, a lower chance of achieving term live birth was observed when a female only indication for IVF was present than when a male/female indication (including unexplained infertility) existed. These findings are congruent with the results of a study by Omland *et al.* [180] in which unexplained infertility was associated with higher live birth rates compared with minimal endometriosis-associated or tubal factor infertility. As shown before [167], women who had received a standard IVF strategy were more likely to reach live birth delivery after a single treatment cycle than women who underwent a mild IVF strategy.

Despite the large sample size, the use of multiple stress measures and the use of live birth as the endpoint, there are some limitations to this study. Only women who were eligible for mild ovarian stimulation combined with the transfer of a single embryo were included. Therefore, it might not be possible to generalize the results of this study to IVF patients with a less favourable prognosis. Furthermore, no records were kept on non-respondents. Based on the average number of couples who undergo IVF treatment

annually in the two participating hospitals and who would qualify for the study (n = 300), the estimated response rate was calculated to be ~65% (391 out of 600). In addition, 19% of the participants could not be analysed due to missing psychological data. In these women, a female factor was more often the cause of infertility. Finally, this study did not measure stress in male patients. The results of the few studies that have addressed stress scores in the male partner also suggest a complex association between infertility-related stress and IVF outcomes [80, 174, 181].

In general, stress is perceived to be detrimental to fertility and outcomes of infertility treatments. Many clinicians as well as researchers implicitly subscribe to the psychogenic model of infertility which can easily result in 'victim blaming' [16]. As a result, couples opting for IVF may downplay their negative emotions, as they often feel dependent on their physicians for their continued treatment participation. The results of this study show that the relationship between psychological variables and IVF success rates is more complex than commonly believed. Patients should not be discouraged to express negative emotions related to infertility and its treatment.

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Chapter 8

General discussion

Introduction

IVF treatment requires the woman to undergo several invasive procedures, which are repeated in subsequent treatment cycles. In addition to the physical burden, the threat of treatment failure confronts the couple with the possibility that they have to give up hope to have a child of their own. In line with the *psychological consequences of infertility* model [16], women seem to experience moderate levels of negative emotions (e.g. distress) before, during and after IVF treatment [30-32, 36, 37, 39-41, 183]. According to another psychological model on infertility and infertility treatment, e.g. the *cyclical model of stress*, patient distress might have a negative influence on IVF pregnancy chance [16, 18]. However, the scientific evidence to support this model is contradictory [31, 80-87].

It has been widely argued that people undergoing IVF should receive infertility counselling by a psychosocial counsellor to help them cope with negative emotions related to treatment and infertility [97]. Hence, the first aim of this study was to evaluate the effect of a psychosocial counselling intervention during IVF treatment on distress in first-time IVF patients in a randomized controlled trial. The results of the few earlier randomized controlled studies on psychosocial counselling interventions did not find a decrease in distress due to counselling. However, effects of counselling might have gone unnoticed due to a limited number of measurements of distress in these studies. In contrast to these earlier studies, distress was measured continuously throughout IVF treatment in the study described in this thesis.

The aim of counselling is to minimize negative emotions related to a stressor (e.g. IVF treatment). An alternative way to decrease distress related to IVF treatment might be to change the stressor. New 'mild' IVF strategies which combine mild ovarian stimulation with single embryo transfer may represent a more patient-friendly approach than standard IVF treatment. Mild ovarian stimulation protocols with gonadotropin-releasing hormone (GnRH) antagonists are likely to be associated with less physical discomfort and psychological distress than standard ovarian stimulation with GnRH agonists [62]. However, the use of mild IVF strategies, which include single embryo transfer, might also be stressful to patients, as patients seem to prefer double embryo transfer to single embryo transfer because of the increased chance of achieving a pregnancy in a given cycle [171]. The combination of GnRH antagonist co-treatment and single embryo transfer was expected to enable patients to have more treatment cycles with additional pregnancy chances in the same time period as standard IVF, due to a shorter cycle duration and possible fewer side effects associated with mild stimulation. This thesis presents the first longitudinal, randomized controlled trial to study not only the clinical and economical consequences, but also the psychological impact of the use of such mild IVF strategies for IVF patients.

The third aim of this thesis was to explore the relation between distress and IVF live birth delivery rates. The popular belief that distress adversely affects IVF outcome may

cause feelings of shame and guilt in IVF patients who do not conceive. A better understanding of the association between distress and IVF outcome might further benefit the emotional adjustment of IVF patients. Whereas most studies in this area report pregnancy rate as the endpoint, the large prospective study presented in this thesis studied the relationship between distress and term live birth.

Can psychosocial counselling alleviate distress related to IVF treatment?

Counselling interventions in infertility treatment focus on expression of emotions and discussion of thoughts related to infertility and its treatment. These interventions are usually characterized by the non-directiveness of the counsellor, the couple format of the sessions and a short duration [56]. In the study described in Chapter 2, counselling was provided by a social worker who is part of the multi-disciplinary IVF team in Rotterdam. In our clinic, psychosocial counselling is optional for all IVF patients during all stages of IVF treatment. The social worker provides counselling in line with the principles of the Experiential Psychosocial Therapy [99]. The central focus of Experiential Psychosocial Therapy is the way individuals relate to others. Even though women have to undergo most of the invasive procedures related to IVF treatment, infertility is a shared problem of both male and female partners. The shared experience of infertility might bring partners closer together, as they are forced to talk about emotional and existential aspects of life [184]. However, men and women often cope differently with childlessness and the stress related to infertility treatment, which may put pressure on the partner relationship. Furthermore, difficulties in partner communication lead to higher distress after unsuccessful fertility treatment in both women and men [185]. Therefore, the counselling intervention studied in this thesis, was targeted at both partners. During the counselling sessions couples were invited to express their feelings and discuss their thoughts on topics related to infertility and IVF treatment, such as coping strategies and the availability of social support, patient-physician communication, decision-making related to IVF treatment, anticipation on possible treatment outcomes and alternatives to IVF (e.g. adoption).

Consistent with previous studies [60, 61], our counselling intervention hardly influenced the amount of distress women experienced during their first cycle of IVF treatment. Furthermore, counselling did not seem to influence distress experienced by male partners either [104]. At pregnancy testing however, women who had received additional psychosocial counselling expressed less negative affect than women who had received routine care and no additional psychosocial counselling. Although this difference was marginally significant, this result might still indicate that our psychosocial counselling intervention succeeded in reducing unrealistic expectations women might have about IVF

success rates. As male partners did not keep a distress diary during treatment, no group comparisons could be made.

The data presented in this thesis indicate that most couples do not think they need additional psychosocial counselling during their first IVF treatment cycle. Furthermore, men were less likely than women to be interested in additional counselling by a social worker. It is possible that more couples would have participated in our study if the timing of the counselling sessions had been different. We chose to offer counselling during the IVF stages which couples usually perceive to be the most distressing, e.g. before the start of the first treatment cycle, during the waiting period and then again after completion of the first cycle. During these stages patients usually do not have medical appointments. Since couples were already required to make several hospital visits during IVF treatment, work or other obligations might have prevented them to take additional time off for the counselling sessions. Furthermore, the semi-structured interviews that were performed after completion of the first IVF cycle suggest that women might want to focus on the medical aspects rather than on the possibly negative psychological consequences of treatment during a first cycle. However, some participants who had not received additional counselling, in hindsight reported the need for contact with the IVF staff during the waiting period or after a failed IVF cycle. Psychosocial counselling might more easily be accepted by veteran IVF patients, as they are more aware of the psychological impact of IVF treatment [59]. First-time IVF patients might more readily accept interventions that integrate both medical and psychosocial aspects of infertility treatment. Moreover, educational interventions which focus on information provision and skills training seem to lead to more positive changes in infertile people than counselling interventions [56]. In contrast to counselling interventions, educational interventions are often carried out in a group format with a higher number of structured sessions. Each of these unique characteristics could explain why educational interventions might be more beneficial to infertile people's well being than psychosocial counselling [56]. However, the current evidence only moderately supports the effectiveness of such psychosocial interventions in reducing patient distress [56]. Hence, alternative ways to decrease distress related to IVF treatment should also be considered.

Does a mild strategy in IVF result in less treatment-related distress?

The psychological consequences of one cycle of mild IVF

Mild treatment strategies in IVF avoid pituitary downregulation with GnRH agonists, which was found to be associated with headache, abdominal pain, painful muscles, and symptoms of depression (Chapter 4). During most stages of the first IVF cycle, mild ovarian stimulation did not lead to a different level of physical complaints or psychologi-

cal distress than conventional stimulation. However, as the average cycle duration was shorter for mild stimulation protocols, women suffered from physical and psychological discomfort for a shorter period of time during one cycle. The shorter and less burdensome period of treatment associated with mild stimulation may also explain why cycle cancellation during the first IVF cycle was associated with a more positive and less negative mood in mild IVF than in standard IVF.

During one stage of the first IVF treatment cycle the mild IVF approach resulted in higher distress levels than the standard strategy, e.g. the day of oocyte retrieval. Mild ovarian stimulation usually leads to the growth and retrieval of fewer oocytes than long-protocol stimulation, which may have influenced the perceived chance of treatment success in some women. Comparisons of the number of oocytes harvested with women using standard ovarian simulation may have resulted in doubts about the effectiveness of mild stimulation. During the semi-structured interviews that were also performed as part of this study, women occasionally raised concerns about the effectiveness of the mild treatment protocol. These doubts usually concerned the lower success rate per transfer associated with single embryo transfer, rather than the perceived effectiveness of mild ovarian stimulation. However, during the IVF stages subsequent to the day of oocyte transfer, distress levels associated with the mild IVF strategy were comparable with the standard IVF strategy. Even though worries about the effectiveness of mild IVF strategies might still have been present, these did apparently not lead to increased distress in women during the final stages of their first IVF cycle.

The psychological consequences of prolonged mild IVF treatment

In chapter 5 it was shown, that overall patient discomfort during the first year of treatment was similar among the two strategies, even though the average number of treatment cycles per couple was higher in mild IVF. However, the level of distress and self-reported physical complaints associated with the mild strategy were stable over time, whereas the level of patient discomfort related to standard IVF increased during subsequent treatment cycles [68]. Furthermore, treatment failure was associated with less distress in mild IVF than in standard IVF treatment (chapter 6). As it seems reasonable to assume that the losses related to treatment failure (fertility, self-esteem, social status etc.) are the same for both strategies, the latter finding suggests that the distress women experience due to IVF treatment failure not only results from the threat of infertility, but also from IVF treatment itself. According to the cognitive dissonance theory [186], people will value their goal more if it is harder to reach. In line with this theory, one could hypothesize that these people are more likely to experience higher distress when this goal cannot be reached than people who invested less in the achievement of the same goal. The fact that women who underwent the standard IVF strategy were more distressed at treatment failure, might suggest that overall, standard IVF was related to more treatment-related discomfort

and distress than mild IVF. Interestingly, distress levels were comparable in conceiving women using either strategy, which might suggest that the achievement of pregnancy neutralizes differences in treatment-related distress.

Does patient distress result in lower live birth rates?

According to the *cyclical model of infertility and stress*, the chance of conceiving through IVF is negatively influenced by high levels of psychological distress [16, 18]. Surprisingly, we found that women who reported a low level of pretreatment distress were less likely to achieve term live birth than women who expressed a moderate level of distress (Chapter 7). Still, as the majority of participating women did not meet the criteria for either clinical depression or anxiety, the results of this thesis do not rule out that high patient distress leads to worse IVF outcomes than moderate distress. In contrast to pretreatment distress, distress related to ovarian stimulation was not associated with live birth delivery chance.

This study is not the first to find a positive association between distress and IVF outcomes, but results of these studies are not often cited by other researchers in this field. Merari and colleagues [181] found that couples who showed strong negative emotional reactions to IVF treatment 10-15 day prior to its initiation had a higher chance of conceiving. Likewise, Cooper and colleagues [174] reported that couples who got pregnant during their first IVF cycle expressed more infertility-related stress before treatment than non-conceiving couples. In another study, women with either extremely high or low scores for anxiety prior to the start of treatment were more likely to get pregnant [82]. A study of the influence of dietary sodium restriction on anxiety in women undergoing IVF showed a higher increase in both state and trait anxiety during treatment in conceiving women as compared to women who did not conceive, which was not influenced by dietary sodium restriction [187]. Finally, Demyttenaere and colleagues [188] found an association between increased depressive symptoms prior to the start of treatment and higher pregnancy rates 12 months later in participants with a male indication for IVF.

Apparently, the relationship between patient distress and IVF success rates is not as straightforward as commonly believed by researchers, clinicians and patients. This relationship might be curvilinear, rather than linear. The results obtained from an exploratory analysis of our data also hinted at such an association. Both extremely high and extremely low levels of distress seemed to be associated with adverse IVF outcomes. The expression of extreme low levels of distress may reflect a tendency to repress awareness of negative emotions caused by IVF treatment. People who use repressive coping strategies tend to selectively avoid attending to threat-related stimuli and also tend to interpret threat-related information in a non-threatening way, including their own physiological

activity, behaviour and cognitions, as well as external stimuli [189]. People who use this coping style describe themselves as non-emotional and rational [190]. Indeed, IVF patients have been shown to use defensive coping styles, possibly related to the fear that the expression of distress may lead to discontinued treatment participation or to treatment failure [93, 175]. Whereas repressors usually exhibit low levels of self-reported distress, they often have high levels of physiological distress, especially in the presence of social evaluation [191]. For example, repressors have been shown to exhibit similar high cortisol levels [192] as highly anxious people. Future studies are needed to explore the possible association between distress, repressive coping strategies and IVF outcomes.

Study limitations and directions for future research

The studies described in this thesis have several strengths (e.g. randomized controlled trials, validated questionnaires) and several limitations. As with many psychological studies in the IVF field, both randomized controlled trials described in this thesis suffered from a high drop-out rate. This might have introduced a reporting bias, as women who experienced high distress might have been less inclined to fill in questionnaires. However, study drop-outs did not report higher levels of distress at the initiation of IVF treatment than women who completed the study. Still, the statistical power of the study described in Chapter 6 might be limited, as this study also suffered from a low response rate. It is possible that women who were the most vulnerable to experience distress during IVF treatment were not included in this study. Therefore, the results of this study should be interpreted with caution. Another limitation of both trials presented in this thesis, is the short length of the follow-up period (e.g. one week after treatment failure). A longer follow-up period is needed to determine the long-term psychological consequences of mild IVF as well as the effects of psychosocial counselling on distress. Women experience distress related to unsuccessful infertility treatment up to six months after treatment termination [41].

In this thesis, both general measures as well as an infertility-specific questionnaire were used to measure distress. Whereas most other studies on psychological aspects of IVF treatment only use retrospective questionnaires, the studies described in this thesis also used diary measures to assess distress. Nevertheless, even the infertility-specific diary measure used in these studies might not have been sensitive enough to determine specific psychological consequences of IVF treatment or infertility counselling. Furthermore, self-report distress questionnaires tap into one aspect of human emotions, e.g. the subjective experience. However, emotions are believed to be made up of multiple components, including cognitions, physiological responses and behavioural reactions [193]. Responses in these different domains may not always be in concordance. Some people may report

low distress levels in stressful conditions, even though they show signs of heightened physiological distress (e.g. heightened heart rate). Although such response dissociation may reflect social-desirability bias, it may also indicate the use of emotion-focused coping strategies which are aimed at emotion-regulation, such as repression. Future studies that aim to test the *cyclical model of infertility and stress* should therefore not only incorporate distress measures, but also measures of coping strategies. Ideally, both self-report measures and biological markers of distress should be included in such studies. Considering the results of the present thesis, it would be highly interesting to investigate associations between distress, repressive coping strategies and IVF outcomes, using proxy measures, observational measures and physical measures apart from self-report questionnaires.

Clinical implications

Despite study limitations, the results of this thesis do not support the provision of routine counselling by a psychosocial counsellor for all first-time IVF patients. We believe psychosocial interventions should only be offered to those people who are the most vulnerable to distress and therefore are most likely to benefit from additional care. However, studies of possible predictors of distress related to IVF treatment are scarce [43]. Although there are some studies that link psychological factors, such as personality [194], relationship characteristics [185], and coping [185] with increased distress in IVF patients, further study of these associations is warranted. Such studies may promote early identification and referral of women who are at risk for psychological problems during treatment.

The data presented in this thesis provide the first evidence that overall, the use of a mild IVF treatment strategy leads to less patient distress than standard IVF treatment. Do these findings imply that the use of mild IVF strategies should be made into the new standard? Some authors have argued that the physician who performs the IVF treatment should determine the maximum number of embryos transferred. According to these authors, physicians have a professional responsibility for the welfare of the future child, because of his or her causal and intentional contribution to IVF treatment and its outcome, including problems related to multiple embryo transfer [195]. Other authors claim that practice standards which are aimed at minimizing multiple pregnancies compromise patient autonomy. They argue that infertile couples have the right to make educated treatment decisions [196]. However, women who attend infertility clinics usually do not possess the knowledge about the specific risks associated with multiple pregnancies to be truly able to make educated decisions. When informed of the actual risks related to multiple gestations, women seem to be less wishful of a twin pregnancy [197]. Still, the majority of women undergoing IVF/ICSI would not prefer single embryo transfer if this procedure led to even the smallest reduction in pregnancy rates [198]. However, most

women who prefer single embryo transfer in the absence of a difference in pregnancy rates, would be willing to undergo an additional treatment cycle, if needed [198]. The results of this thesis show that the combination of single embryo transfer and mild ovarian stimulation can result in similar cumulative term live birth rates over one year of IVF treatment compared to standard stimulation with two embryo transfer, while significantly reducing multiple pregnancy rates. This information, as well as the scientific evidence for the psychological advantages of the use of mild IVF strategies presented in this thesis, might change preferences in favour of mild IVF in patients.

Clearly, fertility physicians need to be aware of the importance of counselling patients regarding the implications and decision-making related to IVF treatment. Counselling should not only entail information about term live birth rates and medical risks associated with different IVF treatment strategies for both mother and child. Physicians should also educate patients about the psychological (and social) aspects of infertility and its treatment to enable them to make educated treatment-related decisions. As the findings of this thesis show, the psychological consequences of different treatment strategies differ during different treatment stages. Therefore, personalised counselling by physicians should be a continuing process throughout all IVF stages, including treatment termination. Increased knowledge of the psychological aspects of infertility in physicians might also lead to an earlier detection of psychosocial problems in IVF patients. Moreover, adopting the *psychological consequences model of infertility* rather than the *cyclical model of stress* will prevent patients from feeling shame or guilt about (possible) future treatment failure. Patients who feel free to express negative emotions about their infertility and infertility treatment to their physician might be open to a referral to a social worker or psychologist, when needed.

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Summary

Chapter 1

IVF treatment requires the woman to undergo several invasive procedures, which are repeated in subsequent treatment cycles. In addition to the physical burden, the threat of treatment failure confronts the couple with the possibility that they may have to give up hope to have a child of their own. In line with the *psychological consequences of infertility* model, women seem to experience moderate levels of negative emotions (e.g. distress) before, during and after IVF treatment. According to another psychological model on infertility and infertility treatment, e.g. the *cyclical model of stress*, patient distress might have a negative influence on IVF pregnancy chance. However, the scientific evidence to support this model is contradictory.

It has been widely argued that people undergoing IVF should receive infertility counselling by a psychosocial counsellor to help them cope with negative emotions related to treatment and infertility. Hence, the first aim of this study was to evaluate the effect of a psychosocial counselling intervention during IVF treatment on distress in first-time IVF patients in a randomized controlled trial. The results of the few earlier randomized controlled studies on psychosocial counselling interventions did not find a decrease in distress due to counselling. However, effects of counselling might have gone unnoticed due to limited number of measurements of distress in these studies. In contrast to these earlier studies, distress was measured continuously throughout IVF treatment in the study described in this thesis.

The aim of counselling is to minimize negative emotions related to a stressor (e.g. IVF treatment). An alternative way to decrease distress related to IVF treatment might be to change the stressor. New 'mild' IVF strategies which combine mild ovarian stimulation with single embryo transfer may represent a more patient-friendly approach than standard IVF treatment. Mild ovarian stimulation protocols with gonadotropin-releasing hormone (GnRH) antagonists are likely to be associated with less physical discomfort and psychological distress than standard ovarian stimulation with GnRH agonists. However, the use of mild IVF strategies, which include single embryo transfer, might also be stressful to patients, as patients seem to prefer double embryo transfer to single embryo transfer because of the increased chance of achieving a pregnancy in a given cycle. The combination of GnRH antagonist co-treatment and single embryo transfer was expected to enable patients to have more treatment cycles with additional pregnancy chances in the same time period as standard IVF, due to a shorter cycle duration. This thesis presents the first randomized controlled trial to study not only the clinical and economical consequences, but also the psychological impact of the use of such mild IVF strategies for IVF patients.

The third aim of this thesis was to explore the relation between distress and IVF live birth delivery rates. The popular belief that distress adversely affects IVF outcome may cause feelings of shame and guilt in IVF patients who do not conceive. A better under-

standing of the association between distress and IVF outcome might further benefit the emotional adjustment of IVF patients. Whereas most studies in this area report pregnancy rate as the endpoint, this thesis studies the relationship between distress and term live birth.

Chapter 2

The objective of the study described in this chapter was to evaluate a psychosocial counselling intervention for first-time IVF couples. In this chapter the impact of this intervention on women's distress is presented. Two hundred and sixty-five couples admitted to an IVF treatment programme at the Erasmus MC were asked to participate in this study. Eighty-four couples agreed and were randomized according to a computer-generated random-numbers table into either a routine-care control group or an intervention group. The intervention consisted of three sessions with a social worker trained in experiential psychosocial therapy: one before, one during and one after the first IVF cycle. Distress was measured daily during treatment by the Daily Record Keeping Chart. Depression and anxiety were measured before and after treatment by the Hospital Anxiety and Depression Scale. We did not find significant group differences on any of these psychological variables. The results of this study do not support the implementation of our counselling intervention for all first-time IVF couples. Furthermore, the low response rate suggests that there is little perceived need for psychosocial counselling among couples during a first IVF treatment cycle.

Chapter 3

In this chapter, the methodological considerations related to a study comparing the effectiveness, health economics and patient discomfort of two IVF treatment strategies are discussed. A randomized controlled clinical trial was performed in two large Dutch IVF centres. The tested treatment strategies were: mild ovarian stimulation [including gonadotrophin-releasing hormone (GnRH) antagonist co-treatment] together with the transfer of one embryo, versus conventional stimulation (with GnRH agonist long protocol co-treatment) and the transfer of two embryos. Outcome measures were: (i) pregnancies resulting in term live birth; (ii) total costs per term live birth; and (iii) patient stress/discomfort per started IVF treatment, over a 12 month period. Power considerations for this study were an overall cumulative live birth rate of 45% for the conventional treatment strategy, with non-inferiority of the mild treatment strategy defined as a live birth rate no more than 12.5% lower than the conventional study arm. For a power of 80% and

alpha of 0.05, 400 subjects were required. As planned, from February 2002 until February 2004, 410 patients were enrolled. This effectiveness study applied an integrated medical, health economics and psychological approach with term live birth over a given period of time after starting IVF as the end-point. Complete and timely patient enrolment has vindicated many of the design decisions.

Chapter 4

The objective of the study in Chapter 4 was to assess the psychological implications of mild ovarian stimulation combined with single embryo transfer (SET) during a first In Vitro Fertilization (IVF) cycle. We conducted a randomized controlled two-centre trial. Three hundred and ninety-one couples were randomized to undergo either mild ovarian stimulation with GnRH antagonist co-treatment and SET (n = 199) or conventional GnRH agonist long protocol ovarian stimulation with double embryo transfer (DET) (n = 192). Women completed the Hospital Anxiety and Depression Scale, the Hopkins Symptom Checklist and the Subjective Sleep Quality Scale at baseline, on the first day of ovarian stimulation and following embryo transfer. Affect was assessed daily with the Daily Record Keeping Chart (DRK) from the first day of ovarian stimulation until the day treatment outcome became known. The conventional IVF group experienced elevated levels of physical and depressive symptoms during pituitary downregulation. At oocyte retrieval, this group experienced more positive affect and less negative affect than the mild IVF group. In the conventional IVF group, cycle cancellation was associated with less positive and more negative affect. In conclusion, mild ovarian stimulation and SET does not lead to more psychological complaints than conventional IVF during the first IVF treatment cycle.

Chapter 5

In this chapter, we aimed to test the hypothesis that mild IVF treatment can achieve the same chance of a pregnancy resulting in term live birth within 1 year as standard treatment, and can also reduce patients' discomfort, multiple pregnancies, and costs. We did a randomized, non-inferiority effectiveness trial. 404 patients were randomly assigned to undergo either mild treatment (mild ovarian stimulation with gonadotropin-releasing hormone [GnRH] antagonist co-treatment combined with single embryo transfer) or a standard treatment (stimulation with a GnRH agonist longprotocol and transfer of two embryos). Primary endpoints were proportion of cumulative pregnancies leading to term live birth within 1 year after randomization (with a non-inferiority threshold of −12.5%),

total costs per couple up to 6 weeks after expected date of delivery, and overall discomfort for patients. Analysis was by intention to treat. The proportions of cumulative pregnancies that resulted in term live birth after 1 year were 43.4% with mild treatment and 44.7% with standard treatment (absolute number of patients = 86 for both groups). The lower limit of the one-sided 95% CI was −9.8%. The proportion of couples with multiple pregnancy outcomes was 0.5% with mild IVF treatment versus 13.1% ($P < 0.0001$) with standard treatment, and mean total costs were € 8333 and € 10 745, respectively (difference € 2412, 95% CI 703–4131). There were no significant differences between the groups in the anxiety, depression, physical discomfort, or sleep quality of the mother. Over 1 year of treatment, cumulative rates of term live births and patients' discomfort are much the same for mild ovarian stimulation with single embryos transferred and for standard stimulation with two embryos transferred. However, a mild IVF treatment protocol can substantially reduce multiple pregnancy rates and overall costs.

Chapter 6

In this study, the impact of treatment failure after two or more cycles on stress was studied, following treatment with a mild versus a standard treatment strategy. Women were randomized to undergo mild ovarian stimulation (including GnRH antagonist co-treatment) and single embryo transfer ($n = 197$) or standard GnRH agonist long-protocol ovarian stimulation with double embryo transfer ($n = 194$). Participants completed the Hospital Anxiety and Depression Scale prior to commencing treatment and 1 week after the outcome of their final treatment cycle was known. Data from women who underwent two or more IVF cycles were subject to analysis ($n = 253$). Women who experienced treatment failure after standard IVF treatment presented more symptoms of depression 1 week after treatment termination than women who had undergone mild IVF: adjusted mean (± 95% confidence interval) = 10.2 (± 2.3) versus 5.4 (± 1.8), respectively, $P = 0.01$. Failure of IVF treatment after a mild treatment strategy may result in fewer short-term symptoms of depression than failure after a standard treatment strategy. These findings may further encourage the application of mild IVF treatment strategies in clinical practice.

Chapter 7

The objective of the current study was to determine whether pretreatment or procedural psychological variables in women undergoing a first IVF cycle affect their chances of having a live birth from that cycle. Between February 2002 and February 2004, 391 women with an indication for IVF were recruited at two University Medical Centres in

The Netherlands. Pretreatment anxiety and depression were measured with the *Hospital Anxiety and Depression Scale*. The *Daily Record Keeping Chart* was used to measure negative and positive affect. Women completed the DRK daily for 1 week, starting on the day of the planning consultation and again daily during ovarian stimulation. Multiple stepwise forward logistic regression analysis was performed with term live birth as the dependent variable. Independent variables included all psychological variables, age, duration of infertility, cause of infertility and type of treatment. Women who reported low negative affect at baseline were less likely to have a live birth than women who reported a moderate level of negative affect ($P = 0.03$). After one IVF cycle, women who received a standard IVF strategy were more likely to have a live delivery than those who received a mild IVF strategy ($P = 0.002$). A male/female indication for IVF was associated with a higher chance of term live birth than a female-only indication ($P = 0.03$). In conclusion, expressing moderate negative emotions before starting IVF might not be always harmful for outcomes.

Chapter 8

In Chapter 8, the main findings of this thesis are discussed. Also, implications for future treatment and research are given. The results of this thesis show that the combination of single embryo transfer and mild ovarian stimulation can result in similar cumulative term live birth rates over one year of IVF treatment as standard stimulation with two embryo transfer, while significantly reducing multiple pregnancy rates. Furthermore, the data presented in this thesis provide the first evidence that overall, the use of a mild IVF treatment strategy leads to less patient distress during treatment than standard IVF treatment. This information might change preferences in favour of mild IVF in patients.

The results of this thesis do not support the provision of routine counselling by a psychosocial counsellor for all first-time IVF patients. We believe psychosocial interventions should only be offered to those people who are the most vulnerable to distress and therefore are most likely to benefit from additional care. Fertility physicians need to be aware of the importance of counselling patients regarding the implications and decision-making related to IVF treatment. Counselling should not only entail information about term live birth rates and medical risks associated with different IVF treatment strategies for both mother and child. Physicians should also educate patients about the psychological (and social) aspects of infertility and its treatment to enable them to make educated treatment-related decisions. As the findings of this thesis show, the psychological consequences of different treatment strategies differ during different treatment stages. Therefore, personalised counselling by physicians should be a continuing process throughout all IVF stages, including treatment termination. Increased knowledge of the psychological

aspects of infertility in physicians might also lead to an earlier detection of psychosocial problems in IVF patients. Moreover, adopting the *psychological consequences model of infertility* rather than the *cyclical model of stress* will prevent patients from feeling shame or guilt about (possible) future treatment failure. Patients who feel free to express negative emotions about their infertility and infertility treatment to their physician might be open to a referral to a social worker or psychologist, when needed.

Samenvatting

Hoofdstuk 1

Wanneer een vrouw met een IVF-behandeling begint moet zij verschillende invasieve procedures ondergaan, die worden herhaald in de daaropvolgende behandelcycli. De behandeling is niet alleen lichamelijk belastend, maar confronteert het paar ook met het feit dat zij de hoop op een kind voorgoed moeten opgeven wanneer de behandeling niet succesvol is. Overeenkomstig het *psychologische gevolgen van onvruchtbaarheid*-model blijken vrouwen een matig niveau van negatieve emoties (*distress*) te ervaren voor, tijdens en na afloop van een IVF-behandeling. Volgens een ander psychologisch model van onvruchtbaarheid, het *cyclische stressmodel*, heeft de *distress* die een patiënt ervaart, mogelijk een negatieve invloed op de zwangerschapskans na IVF. De resultaten van het wetenschappelijk onderzoek op dit gebied zijn echter tegenstrijdig.

Een groot aantal auteurs en deskundigen heeft beargumenteerd dat mensen die IVF ondergaan, standaard zouden moeten worden gecounseld op het gebied van onvruchtbaarheid door een psychosociale hulpverlener. Deze hulpverlener zou hen op deze manier kunnen helpen omgaan met de negatieve emoties die zij ervaren als gevolg van hun onvruchtbaarheid en de behandeling hiervan. Hieruit volgt het eerste doel van dit proefschrift: het evalueren van een psychosociale counselinginterventie die werd aangeboden aan patiënten tijdens hun eerste IVF-behandeling. In een aantal eerdere gerandomiseerde studies bleek counseling niet tot een afname van *distress* te leiden. In deze onderzoeken werd het effect van counseling mogelijk gemist door het beperkte aantal *distress*-metingen. In tegenstelling tot deze eerdere studies werd *distress* in de studie die in dit proefschrift wordt beschreven dagelijks gemeten tijdens de IVF-behandeling.

Het doel van onvruchtbaarheidscounseling is het verminderen van negatieve emoties die het gevolg zijn van een stressor (d.i. IVF-behandeling). Een alternatieve manier om het *distress*-niveau te verlagen is het veranderen van de stressor. Nieuwe milde IVF-behandelprotocollen, waarin een mild stimulatieprotocol met het terugplaatsen van één embryo (SET) wordt gecombineerd, bieden mogelijk een patiëntvriendelijk alternatief voor standaard behandelprotocollen. Milde ovariële hyperstimulatie met GnRH-antagonisten leidt waarschijnlijk tot minder lichamelijke en psychologische klachten dan standaard ovariële hyperstimulatie met GnRH-agonisten. Aan de andere kant zou het gebruik van milde behandelprotocollen stressvol kunnen zijn voor patiënten voor wie de zwangerschapskans per behandelcyclus belangrijk is. Zij blijken vaak de voorkeur te geven aan het terugplaatsen van twee embryo's in plaats van één embryo vanwege de hogere zwangerschapskans per behandelcyclus. Door het terugplaatsen van één embryo met milde ovariële hyperstimulatie te combineren kan mogelijk een hoger aantal behandelcycli met bijbehorende zwangerschapskansen per tijdseenheid worden bereikt in vergelijking met een standaard IVF-behandeling, dit vanwege een kortere cyclusduur. In dit proefschrift wordt de eerste gerandomiseerde gecontroleerde studie gepresenteerd waarin niet alleen

de klinische en economische uitkomsten, maar ook de psychologische gevolgen voor patiënten van het gebruik van milde behandelprotocollen werden bestudeerd.

Het derde doel van dit proefschrift was het exploreren van de relatie tussen *distress* en de kans op een levend geboren kind na IVF. Er wordt vaak gedacht dat *distres*s de resultaten van een IVF-behandeling negatief beïnvloedt, wat schaamte en schuldgevoelens kan oproepen bij die mensen die niet zwanger raken door middel van IVF. Meer duidelijkheid over deze relatie draagt mogelijk bij aan de emotionele verwerking van mensen die een IVF-behandeling ondergaan. In tegenstelling tot eerdere studies, waarin de relatie tussen *distress* en zwangerschapskans werd bestudeerd, wordt in dit proefschrift de relatie tussen *distress* en de kans op een levend geborene onderzocht.

Hoofdstuk 2

Het doel van de studie die in dit hoofdstuk wordt besproken, was het evalueren van een psychosociale counselinginterventie voor paren die aan hun eerste IVF-behandeling beginnen. In dit hoofdstuk wordt de invloed onderzocht die deze interventie heeft op de *distress* die vrouwen ervaren tijdens de behandeling. 265 paren die waren doorverwezen naar een IVF-kliniek werden gevraagd deel te nemen aan deze studie. 84 paren stemden hiermee in en werden gerandomiseerd in A) een routine zorg controlegroep, versus B) een interventiegroep. Deze interventie bestond uit drie gesprekken met een maatschappelijk werker die is getraind in de Ervaringsgerichte Psychosociale Therapie. De gesprekken vonden plaats voor, tijdens en na afloop van de eerste IVF-behandelcyclus. *Distress* werd gedurende de behandelcyclus dagelijks gemeten met behulp van de *Daily Record Keeping Chart*. Depressieve en angstige gevoelens werden zowel voor als na afloop van de behandelcyclus vastgesteld met de *Hospital Anxiety and Depression Scale*. Op geen enkele van de psychologische uitkomstmaten werden significante verschillen gevonden tussen de twee groepen. De resultaten van deze studie lijken het standaard aanbieden van onze interventie tijdens de eerste behandelcyclus niet te rechtvaardigen. Het lage responspercentage lijkt er bovendien op te wijzen dat paren weinig behoefte hebben aan aanvullende psychosociale counseling vlak voor hun eerste behandelcyclus.

Hoofdstuk 3

Dit hoofdstuk beschrijft het design van een studie waarin een evaluatie plaatsvindt van de effectiviteit, de kosten en de patiëntvriendelijkheid van twee IVF-behandelprotocollen, die verschillen in zowel het stimulatieprotocol als het terugplaatsingsbeleid. Het betreft een gerandomiseerd gecontroleerd onderzoek, dat is uitgevoerd in twee grote IVF-centra

in Nederland. De twee onderzochte strategieën waren: A) milde ovariële hyperstimulatie (met GnRH-antagonist) samen met het terugplaatsen van één embryo, versus B) een conventioneel ovarieel hyperstimulatieprotocol (met een lang GnRH-agonist protocol) en het terugplaatsen van twee embryo's. De primaire studie-eindpunten waren: (1) zwangerschap binnen een jaar na randomisatie resulterend in een à terme levend geborene, (2) de totale kosten per paar en kind tot zes weken na de uitgerekende datum, en (3) het totale patiëntenongemak binnen een jaar na randomisatie. Bij de powerberekening van deze studie is er uitgegaan van een overall cumulatieve zwangerschapskans van 45% met de conventionele behandelstrategie en non-inferioriteit van de milde behandelstrategie (gedefinieerd als een verschil van gelijk aan of kleiner dan 12,5% in de ondergrens van de kans op een levend geborene in vergelijking met de conventionele behandelstrategie). Voor een power van 80% en een alpha = 0,05 moesten 400 deelnemers worden geïncludeerd. Volgens plan werden tussen februari 2002 en maart 2004 410 patiënten geïncludeerd in de studie.

Hoofdstuk 4

De doelstelling van de studie in hoofdstuk 4 was het vaststellen van de psychologische gevolgen van milde ovariële stimulatie in combinatie met het terugplaatsen van één embryo tijdens een eerste IVF-behandelcyclus. Er werd een gerandomiseerde gecontroleerde studie uitgevoerd in twee IVF-centra. 391 paren werden gerandomiseerd voor behandeling met: A) milde ovariële hyperstimulatie (met GnRH-antagonist) in combinatie met het terugplaatsen van één embryo (n = 199), versus B) conventionele ovariële hyperstimulatie (met een lang GnRH-agonist protocol) en het terugplaatsen van twee embryo's (n = 192). De deelneemsters vulden op de volgende tijdstippen een aantal vragenlijsten in: 1) op de dag van de intake, 2) op de dag dat zij met de ovariële stimulatie begonnen en 3) op de eerste dag na het terugplaatsen van het embryo of de embryo's. De volgende vragenlijsten werden afgenomen: de *Hospital Anxiety and Depression Scale*, de *Hopkins Symptom Checklist* en de *Subjective Sleep Quality Scale*. Vanaf de eerste dag dat de deelneemsters met de ovariële stimulatie begonnen tot en met de eerste dag waarop de uitkomst van de behandelcyclus bekend was, werd ook dagelijks hun stemming gemeten met behulp van de *Daily Record Keeping Chart*. De deelneemsters in de conventionele behandelgroep rapporteerden tijdens downregulatie meer lichamelijke en depressieve klachten in vergelijking met de deelneemsters in de milde behandelgroep, die geen downregulatie ondergingen. Op de dag dat de punctie plaatsvond, scoorden de deelneemsters uit de eerste groep echter hoger op positieve stemming en lager wat betreft negatieve stemming dan de milde behandelgroep. Vergeleken met de milde groep, bleek in de conventionele groep het voortijdig staken van de eerste behandelcyclus met

lagere scores voor positieve stemming en hogere scores voor negatieve stemming samen te hangen. Uit deze resultaten kan worden geconcludeerd dat milde ovariële hyperstimulatie (met GnRH-antagonist) in combinatie met het terugplaatsen van één embryo gemiddeld niet tot meer psychologische en lichamelijke klachten leidt tijdens de eerste IVF-behandelcyclus dan het gebruik van een conventioneel behandelprotocol.

Hoofdstuk 5

Het doel van dit hoofdstuk was om vast te stellen of een milde IVF-strategie eenzelfde kans op een à terme levend geborene tot gevolg heeft binnen een jaar in vergelijking met de standaardstrategie, en of deze strategie leidt tot minder meerlingzwangerschappen, minder kosten en minder psychologische en lichamelijke klachten. Er werd een gerandomiseerde en gecontroleerde effectiviteitstudie uitgevoerd met twee onderzoeksgroepen. 404 patiënten werden gerandomiseerd voor behandeling met: A) milde ovariële hyperstimulatie (met GnRH-antagonist) in combinatie met het terugplaatsen van één embryo, versus B) conventionele ovariële hyperstimulatie (met een lang GnRH-agonist protocol) en het terugplaatsen van twee embryo's. De primaire studie-eindpunten waren: (1) zwangerschap binnen een jaar na randomisatie, resulterend in een à terme levend geborene, (2) de totale kosten per paar en kind tot zes weken na de uitgerekende datum, en (3) het totale patiëntenongemak binnen een jaar na randomisatie. De cumulatieve kans op een zwangerschap leidend tot een à terme levend geborene binnen een jaar was 43,4% in de milde groep en 44,7% in de standaardgroep. De kans op een meerlingzwangerschap per paar was respectievelijk 0,5% versus 13,1% ($P < 0{,}001$) en de totale kosten bedroegen € 8.333 versus € 10.745 ($P = 0{,}006$). Binnen een jaar was er geen verschil in de oppervlaktes onder de curve voor angst, depressie, lichamelijke klachten en kwaliteit van slaap. Milde ovariële stimulatie in combinatie met het terugplaatsen van één embryo resulteert in een gelijke cumulatieve kans op een à terme levend geborene en een gelijke hoeveelheid patiëntenongemak na een jaar in vergelijking met de standaardstimulatie in combinatie met het terugplaatsen van twee embryo's. Daarnaast leidt het gebruik van de milde strategie tot minder meerlingzwangerschappen en lagere totale kosten.

Hoofdstuk 6

In deze studie werd onderzocht wat de psychologische impact is van het mislukken van een IVF-behandeling op vrouwen die meer dan één behandelcyclus hebben ondergaan volgens een mild of een standaard behandelprotocol. De deelneemsters werden gerandomiseerd voor behandeling met: A) milde ovariële hyperstimulatie (met GnRH-antagonist)

samen met het terugplaatsen van één embryo (n = 197), versus B) een conventioneel ovarieel hyperstimulatieprotocol (met een lang GnRH-agonist protocol) en het terugplaatsen van twee embryo's (n = 194). Vóór hun eerste behandelcyclus en één week na afloop van hun laatste behandelcyclus vulden de deelneemsters de *Hospital Anxiety and Depression Scale* in. De gegevens van de deelneemsters die meer dan één behandelcyclus ondergingen, werden geanalyseerd (n = 253). De deelneemsters die volgens het standaard behandelprotocol waren behandeld, rapporteerden meer depressieve symptomen nadat hun behandeling was mislukt dan vrouwen die volgens het milde protocol waren behandeld (P = 0,01). De depressieve gevoelens die samenhangen met het mislukken van een IVF-behandeling, lijken te worden beïnvloed door de aard van het gebruikte behandelprotocol.

Hoofdstuk 7

De doelstelling van deze studie was het vaststellen van de invloed van psychologische factoren op de slagingskans van een eerste IVF-poging. Hierbij werd rekening gehouden met de psychologische gesteldheid van de deelneemsters vóór en tijdens de IVF-behandeling. Tussen februari 2002 en februari 2004 werden 391 vrouwen die voor IVF in aanmerking kwamen, geworven in twee universitaire medische centra in Nederland. Symptomen van angst en depressie voorafgaand aan de behandeling werden gemeten met de *Hospital Anxiety and Depression Scale*. Negatieve en positieve stemming werden dagelijks gemeten gedurende één week na de intake en tijdens de ovariële hyperstimulatie met behulp van de *Daily Record Keeping Chart*. Er werd een multipele stapsgewijze voorwaartse regressieanalyse uitgevoerd met de kans op een à terme levend geborene als de afhankelijke variabele. De onafhankelijke variabelen waren: de eerdergenoemde psychologische variabelen, leeftijd, duur van de onvruchtbaarheid, oorzaak van de onvruchtbaarheid en het soort behandelprotocol. Deelneemsters die bij aanvang van de studie weinig negatieve gevoelens rapporteerden, hadden een kleinere kans op een à terme levend geborene dan deelneemsters die een zekere mate van negatieve gevoelens rapporteerden (P = 0,03). Daarnaast bleken deelneemsters die tijdens de eerste behandelcyclus waren behandeld volgens een standaardprotocol, een grotere kans te hebben op een à terme levend geborene dan deelneemsters die volgens een mild protocol waren behandeld (P = 0,002). Wanneer de oorzaak van de onvruchtbaarheid door zowel mannelijke als vrouwelijke factoren kon worden verklaard, was de kans op een à terme levend geborene groter dan wanneer alleen vrouwelijke factoren de onvruchtbaarheid konden verklaren (P = 0,03). De belangrijkste conclusie uit dit onderzoek is dat het uiten van negatieve gevoelens niet altijd tot slechtere IVF-resultaten blijkt te leiden.

Hoofdstuk 8

In hoofdstuk 8 worden de belangrijkste bevindingen uit dit proefschrift besproken. Daarnaast worden de implicaties van deze resultaten voor de praktijk en voor toekomstig onderzoek uiteengezet. Uit het onderzoek dat in dit proefschrift is beschreven, blijkt dat een behandeling die bestaat uit de combinatie van milde ovariële hyperstimulatie (met GnRH-antagonist) en het terugplaatsen van één embryo, na één jaar in een gelijke cumulatieve kans op een à terme levend geborene resulteert als standaardstimulatie in combinatie met het terugplaatsen van twee embryo's. Tegelijkertijd blijkt het gebruik van de milde strategie tot minder meerlingzwangerschappen te leiden. Daarnaast wordt in dit proefschrift voor het eerst wetenschappelijk onderbouwd dat het gebruik van een mild behandelprotocol tijdens en vlak na de behandelperiode minder *distress* bij patiënten veroorzaakt dan het gebruik van het standaardprotocol.

De resultaten van dit proefschrift ondersteunen niet het routinematig aanbieden van adviesgesprekken met een maatschappelijk werker aan alle paren die aan hun eerste IVF-behandelcyclus beginnen. Dergelijke psychosociale interventies zijn slechts geïndiceerd voor echtparen die kwetsbaar zijn en die om deze reden werkelijk baat hebben bij aanvullende zorg. Er is voor fertiliteitsartsen een belangrijke rol weggelegd wat betreft patiëntenvoorlichting met betrekking tot de implicaties van de verschillende behandelkeuzen waar patiënten zich voor zien gesteld. Idealiter heeft deze voorlichting niet alleen betrekking op de zwangerschapskansen en de medische risico's voor moeder en kind van bepaalde behandelingen, maar ook op de psychologische (en sociale) gevolgen van onvruchtbaarheid en de verschillende behandelingen. Op deze manier worden patiënten in staat gesteld om weloverwogen behandelingskeuzen te maken. Aangezien dit proefschrift laat zien dat de psychologische gevolgen van de verschillende behandelingen kunnen verschillen per behandelstadium, lijkt geïndividualiseerde voorlichting tijdens alle stadia van de behandeling op zijn plaats. Artsen die op de hoogte zijn van de psychologische aspecten van onvruchtbaarheidsbehandelingen, zullen mogelijk ook eerder psychosociale problemen bij patiënten signaleren. Wanneer artsen bij hun voorlichting bovendien uitgaan van het *psychologische gevolgen van onvruchtbaarheid*-model in plaats van het *cyclische stressmodel*, voorkomen zij wellicht dat patiënten schuld- en schaamtegevoelens ontwikkelen als gevolg van het mislukken van hun behandeling. Wanneer patiënten zich vrij voelen om hun negatieve gevoelens te uiten met betrekking tot hun onvruchtbaarheid en de behandeling hiervan, staan zij mogelijk ook meer open voor doorverwijzing naar een psychosociale hulpverlener wanneer dit nodig blijkt te zijn.

Publications

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Curriculum vitae

Cora de Klerk is a research psychologist at the Erasmus MC University Medical Centre in Rotterdam, The Netherlands. She received her master's degree in Clinical and Health Psychology from Leiden University in 2001. Her master's thesis focused on the relationship between parental bonding and depressive symptomatology in adolescence. During her studies, she was a research assistant at the Helen Dowling Institute in Utrecht, where she participated in a study evaluating the effect of psychosocial interventions for women with breast cancer. After she graduated, Cora briefly worked at the Parnassia Addiction Research Centre in The Hague. In 2002, she joined the Department of Medical Psychology and Psychotherapy at the Erasmus MC, where she worked on her PhD thesis under the supervision of Prof. Jan Passchier and Prof. Nick Macklon. The main focus of her research is on the psychological consequences of reproductive health problems, and the role of psychosocial interventions to improve outcomes. Other current research projects include studies evaluating psychological interventions for adolescent chronic pain and obesity. Since commencing her PhD, Cora has presented at a number of international conferences. In 2007, her presentation was awarded with the *Fertility Society of Australia Exchange Award* at the *23rd Annual Meeting of the European Society of Human Reproduction and Embryology (ESHRE)*. In addition to research, she is involved in teaching psychology and communication skills in the medical curriculum at the Erasmus MC. Since 2006, Cora has been a member of the *Beraadsgroep Voorplantingsgeneeskunde* of the Erasmus MC, which is an ethics committee on assisted human reproduction.