Title

The impact of a self-administered coping intervention on emotional wellbeing in women awaiting the outcome of IVF treatment: a randomised controlled trial.

Running title

Effect of a self-administered coping intervention

Authors

Henrietta Ockhuijsen[1,*], Agnes van den Hoogen[2], Marinus Eijkemans [3], Nick Macklon[1,4], Jacky Boivin[5]

[1]Department of Reproductive Medicine and Gynaecology, University Medical Centre Utrecht, the Netherlands

[2]Department of Neonatology, Wilhelmina Children's Hospital and University Medical Centre Utrecht, the Netherlands

[3]Julius Centre for Health Science and primary care, University Medical Centre Utrecht, the Netherlands

[4]Academic Unit of Human Development and Health, University of Southampton, United Kingdom

[5]School of Psychology, Cardiff University, United Kingdom

*Correspondence address: e-mail: h.d.l.ockhuysen@umcutrecht.nl

Running title

Effect of a self-administered coping intervention

Abstract

Study Question: The aim of this study was to investigate the effect of the Positive Reappraisal Coping Intervention (PRCI) on anxiety in women awaiting the outcome of an IVF/ICSI cycle.

Summary answer: Women willing to participate in the RCT reported significantly more anxiety during the waiting period than before treatment but the use of the PRCI did not significantly reduce anxiety during the waiting period.

What is known already: Waiting for the outcome of IVF/ICSI treatment after embryo transfer is one of the most stressful periods of fertility treatments. At present, no evidence-based coping interventions are available to assist women though this waiting period. The PRCI has been designed to address this unmet need by promoting positive reappraisal coping.

Study design, size, duration: A three-armed RCT evaluating the PRCI women undergoing IVF/ICSI. Data were collected between October 2010 and June 2012. Participants were randomised to receive either PRCI and emotional monitoring, emotional monitoring only, or routine care. Only the PRCI-monitoring group received the coping intervention, comprising of an explanatory leaflet and 10 statements to be read at least once in the morning and once in the evening.

Participant, materials, setting, methods: To capture the general impact of the PRCI all three groups completed questionnaires at three time points: just before the waiting period (Time 1: stimulation phase), on day 10 of the 14-day waiting period (Time 2: waiting period) and 6 weeks after the start of the waiting period (Time 3: six-week follow-up). In addition, to capture the specific impacts of PRCI on the days of the waiting period the PRCI-monitoring and the monitoring-control group also rated daily, for the 14-day waiting period, their emotions and reactions.

Main results and the role of chance: Three hundred and seventy seven of the women who agreed to participate and met eligibility criteria were randomised. Study participants reported significantly more anxiety and depression during the waiting period than before treatment ($p < 0.001$). Mean difference in anxiety between time 1 versus time 2 was 1.465 (95%CI 1.098 to 1.832). Mean difference in depression between time 1 versus time 2 was: 0.514 (95%CI 0.215 to 0.813). Use of the PRCI did not significantly reduce anxiety or depression, or daily negative emotions during the waiting period. However, patients randomised to PRCI reported significantly more positive emotions during the waiting period ($p<0.001$) than the monitoring-control group, and reported the intervention to be easy to use, and as having a positive psychological effect. No significant differences were found between groups in treatment outcome.

Limitations, reasons for caution: The lack of difference observed in the present study between the PRCI and the monitoring-control could have been due to the effects of monitoring itself or its ability to attenuate or obscure effects of the PRCI intervention in unknown ways. A randomised group of women that used only the PRCI without daily monitoring would provide more insight.

Wider implications of the findings: The PRCI was shown to help women reinterpret the demands of the waiting period in a more positive way. These results are consistent with previous studies showing that positive reappraisal coping is a useful strategy for unpredictable and uncontrollable situations represented by a medical waiting period. This simple low cost self-help coping intervention increases positive affect during the waiting period in an IVF/ICSI treatment.

Study funding/competent interest(s): The Women and Baby Division of the University Medical Centre Utrecht funded the study. The authors have no conflicting interest(s).

Trial registration number: The study is registered at the Clinical Tials.gov (NCT01701011).

Key words

Coping-intervention, Medical waiting period, Randomised Controlled Trial, Anxiety, Positive emotions

Introduction

In health-care patients often have to deal with different waiting periods that could be stressful because the outcome of that period cannot be predicted or controlled, and is often difficult to manage (Boivin and Lancastle, 2010; Lancastle and Boivin, 2008). Theory shows that patients who are waiting for the results of medical treatments or examinations should use meaning-based coping strategies to deal with negative anticipatory emotions (Folkman and Lazarus, 1988). Although medical waiting periods are stressful, research on coping interventions to deal with waiting periods is limited (Phelps et al., 2012).

Meaning-based coping strategies can be helpful in situations that involve a prolonged period of unpredictability and uncertainty. Tedlie Moskowitz et al. (1996) and Folkman and Moskowitz (2000) observed that the use of the coping strategy positive reappraisal, by carers of partners in the final stage of AIDS, led to positive emotions. People who use this strategy try to reinterpret the meaning of the situation so that they can obtain some benefit. Folkman and Lazarus (1988) suggested that the effect of positive emotions is to stimulate people to go on in their efforts to deal with these enduring stressful situations.

Woman undergoing fertility treatment, cope with an unpredictable and uncontrollable waiting period when they wait to find out whether or not treatment is successful. In a cross sectional study among 242 women undergoing fertility treatment, ten significant difficulties were identified like: monthly anticipation of treatment results (40%), lack of spontaneity in sexual relationship (30%), uncertainty regarding the future (29%), not being able to solve the

problem myself (17%) (Benyamini et al., 2005). Research shows that the most stressful parts of a fertility treatment are the waiting period after embryo transfer (ET), doing a pregnancy test and finding out treatment was unsuccessful (Boivin and Takefman, 1995; Eugster and Vingerhoets, 1999; Merari et al., 1992;Verhaak et al., 2010; Yong et al., 2000). Although women have increased anxiety and depressive symptoms during the waiting period after ET (Boivin and Lancastle, 2010; Eugster and Vingerhoets, 1999; Lancastle and Boivin, 2008; Yong et al., 2000) they often do not look for psychological support (Boivin et al., 1999; Van Dongen et al., 2012). Arguments for not searching for professional support are perceived difficulty of scheduling sessions, not knowing who to contact and potential cost of sessions (Boivin et al., 1999). This lack of action occurs despite the fact that women often wonder whether stress influences the outcome of their fertility treatment. Meta-analyses make conflicting conclusions about the role of stress with a lack of effect on single cycles (Boivin et al., 2011) but possible effects on multiple cycles of treatment (Matthiesen et al., 2011). Narrative and meta-analytic reviews about the impact of psychosocial interventions on anxiety, depression and treatment outcome are also inconsistent (Boivin, 2003; Hammerli et al., 2009). Inconsistency in these reviews could be due to the fact that psychosocial interventions are generally aimed at the entire fertility treatment and not on a specific stage like the waiting period after ET. A review found that psychosocial interventions in infertility which emphasized education and skills training that focused on specific targets were more effective than more general interventions which emphasized emotional expression and support (Boivin, 2003).

The Positive Reappraisal Coping Intervention (PRCI) is designed for medical waiting periods such as waiting for the outcome of a fertility treatment. The PRCI consists of a card with ten statements and an information leaflet about the coping strategy which was designed to stimulate the use of positive reappraisal coping. The development of PRCI was in keeping

with the Medical Research Council framework for development of complex interventions: it used theory, integrated empirically validated determinants of behaviour, tested the acceptability and feasibility of the intervention and estimated effect size for future randomised controlled trials on effectiveness (Campbell et al., 2000; Craig et al., 2008). The development of PRCI is described in detail elsewhere (Lancastle, 2006; Lancastle and Boivin, 2008) but is briefly summarized here. Our goal was to develop a coping intervention that was theoretically derived, simple enough for untrained patients to use by themselves (whenever needed), sufficiently inexpensive to be made freely available, and generic so it could be adapted for other health contexts.

From these considerations PRCI was conceptualized using the cognitive model of stress and coping (Folkman, 1997; Folkman, 2011; Lazarus and Folkman, 1984) and the Velten positive mood induction procedures (Velten, 1968). The first pilot study generated the potential pool of statements for the PRCI card. Seventeen items with face validity as intervention items were selected from three existing coping scales (COPE questionnaire, problem-appraisal coping scale and Ways of Coping questionnaire). Two further items ("try to do something meaningful" and "try to do something that makes me feel good") were adapted from a qualitative interview schedule designed to investigate the experience of positive meaningful events (Folkman and Moskowitz, 2000). Seven filler items were also added, each of which represented an alternative way of coping with stressful situations. In the first pilot study 36 patients waiting for assessment or treatment in the Accident and Emergency department were provided with a hypothetical scenario of a patient waiting for important medical test results and asked to imagine themselves in this situation and to rate (for all 26 selected reappraisal and filler coping strategies) whether they would use the strategy, find it helpful, and capable of making them feel more positive during this experience of waiting for important medical test results. The analysis showed discriminant validity with the capacity of positive

reappraisal items to make the patient feel more positive in this situation rated higher than for filler items (i.e., other coping strategies, (t (35) = 2.13, p < .05). As expected from theory, the perceived helpfulness of the positive reappraisal items for this (unpredictable, uncontrollable) medical waiting period was significantly higher then for the filler items (i.e., other coping strategies). There was no gender difference in response to any items (all ps < 0.05) and internal reliability amongst all positive reappraisal items was high (Cronbach alpha 0.89 for beneficial ratings). Given these results, the final selection of the ten PRCI statements was based on optimising percentage of patients endorsing use of the item, correlation with other items, perceived helpfulness and potential for improved positive mood ratings. A second pilot study was conducted to further model the intervention. In this study the psychological wellbeing of medical students who used the PRCI (n=19) while they were waiting for seven days to sit important exams was compared with a control group (n=20) who did not receive the intervention. Students who received the PRCI read the card as instructed (twice per day on average), felt more optimistic about their exam results in the last three days before the exam and reported marginally fewer physical stress reactions (e.g., racing heart, sweaty palms). The acceptability and feasibility of the PRCI was explored in an RCT of 82 women undergoing IVF who were randomly assigned to PRCI, a positive mood induction (PMI) control group ("I feel good") or a daily monitoring control group. The RCT was additionally designed to estimate effect sizes for PRCI effects on coping, appraisals and other psychological factors related to the cognitive model of stress and coping (Lancastle, 2006). Women using PRCI were found to appraise the waiting period as significantly more controllable (F(2, 79)=3.10, p < 0.05) and reported significantly more challenge appraisals (F(2, 79)=2.58, p < 0.05) then the positive mood induction group (Lancastle, 2006).

A feasibility study carried out in the Netherlands for the present study showed that 12/19 women (63%) undergoing IVF found the PRCI was suitable for this context and 17/19 (89.5%) rated PRCI as quick and easy (unpublished data).

These feasibility results suggest that PRCI could be useful for medical waiting periods and that there would be sufficient interest among patients to make feasible a full RCT within the two years available to do a trial. The aim of the present study was to investigate the effect of the PRCI on emotional wellbeing in women awaiting the outcome of an IVF/ICSI cycle. The primary outcome was general anxiety. Secondary outcomes were general depression, treatment specific positive and negative emotions, evaluation of the intervention and treatment outcome. It was hypothesised that PRCI would reduce general and treatment-specific negative emotions in infertile women waiting for the outcome of their fertility treatment compared to control conditions.

Materials and methods

Trial design

The PRCI was evaluated in a three-arm Randomised Controlled Trial (RCT). Participants were randomised to a PRCI-monitoring group or to one of two control groups: monitoring-control or routine care control group. To capture the general impact of the PRCI, all three groups completed anxiety and depression questionnaires at three time points: just before the waiting period (Time 1: pre-intervention), on Day 10 of the 14-day waiting period (Time 2: waiting period intervention) and 6 weeks after the start of the waiting period (Time 3: post-intervention). Mobile phone text reminders were sent to patients regarding completing the Time 1 and Time 3 questionnaires (if necessary) and all patients received a reminder just prior to the Time 2 assessment on the ninth day of the waiting period.

To capture the specific impacts of PRCI on the days of the waiting period, the PRCI-monitoring and the monitoring-control group also rated daily, for the 14-day waiting period, their treatment specific emotions and reactions. Daily monitoring has previously been shown to be an efficient and sensitive way of evaluating emotional reactions during fertility treatment, including the waiting period (Boivin and Takefman, 1995; Boivin and Lancastle, 2010) and to be sensitive to intervention effects during Assisted Reproductive Technologies (ART) (de Klerk et al., 2005). One potential drawback of this method of assessment is that it may impact on the reporting of emotions itself. For example, habituation or sensitisation to monitoring per se may decrease or increase reporting of anxiety compared to groups that do not monitor (Cohen et al., 1995). Due to this potential reactivity the monitoring-control group also monitored emotions and reactions daily during the waiting period. The routine care control group did not receive the intervention and did not monitor daily their reactions, but completed questionnaires as per the other groups.

Participants

The RCT was conducted over a period of twenty months in a fertility clinic at a university hospital in the Netherlands. The sample size calculation for the three-arm RCT was based on the following parameters. To test the difference in psychological wellbeing between three groups with a power of 95%, α=0.05 and a medium effect size (f=0.25), a total of 297 participants was required (99 patients per group) (Polit and Hungler, 1999; Polit and Beck, 2008). Taking into account a 20% attrition rate at least 124 women had to be recruited in each group. Effect size and attrition were derived from Lancastle and Boivin (2008). The inclusion criteria were woman undergoing a stimulated or cryopreserved IVF/ICSI treatment cycle. Women not speaking the Dutch language were excluded.

Intervention and control group

The PRCI-monitoring group received the PRCI. The PRCI is a small card that contains ten positive reappraisal statements and a leaflet with a detailed explanation about this coping approach. See Figure 1 for the PRCI card (contact author JB for complete intervention, including PRCI leaflet). Permission was obtained from Cardiff University to reproduce the PRCI card. The leaflet instructed women to read the PRCI at least twice a day, once in the morning and once in the evening as well as at any other time they felt the need, and to think about how each statement applied to them personally. The other groups did not receive the PRCI.

Materials

Data were obtained with self-reported questionnaires, daily monitoring and from the medical records. The following self-report measures were used:

The Background Information Form (BIF) is a 16-item self-report questionnaire designed to obtain demographic (e.g. age, educational status), medical (e.g. previous illness) and gynaecological (e.g. infertility diagnosis, previous infertility treatment) characteristics. This form was completed by all groups pre-intervention (Time 1).

The Hospital Anxiety and Depression Scale (HADS) was used to measure general anxiety and depression (Zigmond and Snaith, 1983). The HADS consists of 14 items (7 items for each subscale) that are rated on a 4-point Likert scale. The total score is the sum of the 14 items, and for each subscale the score is the sum of the respective seven items (ranging from 0–21). Scores on each scale can be interpreted in ranges: normal (0-7), mild (8-10), moderate (11-14)

and severe (15-21) anxiety and depression. The Dutch version of the HADS has been shown to be a valid and reliable instrument, including in the IVF/ICSI context (de Klerk et al., 2005). All groups completed the HADS at Time 1, Time 2 and Time 3.

The Daily Record Keeping (DRK) form was used to rate positive and negative emotions daily during the 14-day waiting period (PRCI-monitoring and monitoring-control groups only) (Boivin and Takefman, 1995). The DRK was developed for use in fertility treatment and comprises 46 possible reactions to the IVF waiting period, including the 20 positive and negative emotions used in the present analysis. Women endorsed each of the reactions provided on the DRK (e.g., happy, sad, anxious) according to whether, and to what extent, they had felt that way in the previous 24 hours. Emotions were rated on a scale from 0 to 3, with higher scores representing more emotion. These ratings were summed to compute positive and negative emotion subscales that Folkman and Lazarus (1985) proposed to be the emotional counterparts of particular appraisals of a situation. Negative emotions comprised threat (e.g., tense, worried) or harm emotions (e.g., sad, discouraged) whereas positive emotions referred to challenge (e.g., hopeful, positive) or benefit emotions (e.g., content, happy) (Folkman and Lazarus, 1985).

The DRK has been used in numerous treatment studies with the Cronbach alpha for the emotional subscale in the range of 0.76 to 0.82 for subscales (Boivin, 1997). The DRK item on vaginal bleeding (i.e., spotting) was also used and was rated in the same way. This item referred to light bleeding or spotting which occurs during the waiting period in approximately 30% of patients (De Sutter et al., 2006). Vaginal bleeding is not consistently associated with pregnancy outcome (De Sutter et al., 2006) but may nevertheless affect daily emotional reactions due to patient perceptions of the meaning of this symptom. The DRK was translated and used in a Dutch study that showed good correspondence between the original and Dutch

version, and acceptable convergent and discriminant validity with other measures of anxiety and depression (de Klerk et al., 2005). Participants were instructed to complete the DRK at the end of the day and for the PRCI-monitoring-group at least one hour after reading the PRCI card to limit the chance of DRK ratings being artificially and transiently influenced by completing the DRK. The PRCI-monitoring and the monitoring-control groups completed the DRK daily during the two-week waiting period from the day of ET until the day before the pregnancy test. Women also noted on the DRK the number of times per day they read the PRCI.

The Intervention evaluation form (IEF), a 23-item questionnaire developed to assess perceptions of intervention, was used to assess PRCI in previous research (Lancastle and Boivin, 2008). It measures the following aspects of the intervention: practicality (6 items), acceptability (4 items), endorsement and feasibility (4 items), perceived psychological effects (7 items) and perceived duration of intervention effects (2 items). The response scale varies by item. The PRCI-monitoring group completed the intervention evaluation form at Time 2.

A medical chart review at the end of treatment was used to obtain data about treatment outcome: clinical pregnancy and clinical pregnancy with fetal heartbeat. Clinical pregnancy is a pregnancy diagnosed by ultrasonography of one or more gestational sacs or definitive clinical signs of pregnancy (Zegers-Hochschild et al., 2009). Clinical pregnancy with fetal heartbeat is a pregnancy diagnosed by ultrasonography or clinical documentation of at least one fetal with heart beat (Zegers-Hochschild et al., 2009). The medical chart of all groups was examined at six-weeks follow-up.

Procedure

The ethical committee of the University of Utrecht provided ethical review and approval for this study. The opt-in method was used to recruit participants as per requirements of the Ethics Committee. Participants were sent an invitation to the trial and if interested asked to contact the research team using the reply form or email address provided. A researcher contacted patients interested in the study to give more information about the study and answer any questions. Those who decided to participate were sent a written information sheet and a consent form to return in a pre-addressed stamped envelope. During their first visit to the hospital, more information was given about the logistics of the study, as needed, but all patients were given the same information according to a written protocol.

A computer-generated table of random numbers was used to achieve the stratified randomisation of the 372 women who met the eligibility criteria. The type of treatment (stimulated or with use of own cryopreserved embryos from a previous cycle) stratified the population because emotions and expectations relative to a stimulated IVF/ICSI may differ from a cryo-preserved treatment (Provoost et al., 2010; Svanberg et al., 2001). Randomisation took place after the first assessment (Time 1: pre-intervention) between follicle aspiration and ET. An independent researcher was responsible for the randomisation. Participants were not told what intervention was being evaluated, whether it was the intervention card or monitoring form or psychological questionnaires. The independent researcher had no contact with participants after randomisation. All women received written information about group assignment on the day of the ET. They received instructions for the waiting period in an opaque sealed envelope after the ET. The clinical staff that performed the ET was blinded to the content of the envelope. After the ET, there was no further contact between the clinical staff, other patients, or the researcher during the 14-day waiting period. An independent research assistant verified random data input for accuracy of the database.

Statistical methods

IBM SPSS Statistics 20 was used to perform the statistical analysis. Descriptive statistics for means and standard deviations were used to describe baseline variables and outcome of the intervention evaluation. Equivalence of baseline measures between groups was examined by one-way analyses of variance (ANOVA) for normally distributed variables on interval or ratio level and chi-square for variables on nominal level. If the groups were not comparable on demographics, medical history, or gynaecological variables, those variables were employed as covariates or factors in subsequent analyses. The onset of menstrual bleeding during the waiting period could differ between women and therefore vaginal bleeding (i.e., spotting) was used as a covariate in analyses. A mixed model for repeated measures was used to examine the differences between the three groups over time for the primary outcome anxiety and secondary outcomes depression and treatment-specific positive and negative emotions. All models were estimated by the method of restricted maximum likelihood (REML) and the Compound Symmetry covariance structure was chosen for the repeated measures. For the DRK analysis, with 14 repeated measures, we used time as a continuous variable with a linear contrast. The parameter of the convergence criteria was set at 0.000001(absolute). Results for this outcome will be presented as slope over time and differences in slope between groups when a group by time interaction is analysed. The analysis was performed according to intention to treat. The main effect of time indicated change over time (regardless of group), the main effect of group indicated overall differences between groups (regardless of time) and the group by time interaction indicated differences between groups at each time point. One sample t-tests were used to test whether evaluations of the intervention within the PRCI-monitoring group were significantly different from the ‘no effect’ rating.

Results

Recruitment, participant flow and baseline data

Figure 2 shows the study flow chart. In the 20 months of recruitment, between October 2010 and June 2012, 1445 letters were sent to women with an invitation to the trial. Of the 565 women who replied via a letter or email, 188 (33%) were not eligible. See Figure 2 for the main reasons of non-eligibility. The remaining 377 women were randomised and the 349 who had an embryo to transfer (n=119 PRCI-monitoring, n=117 monitoring-control, n=113 routine care control) received an opaque sealed envelope after transfer with detailed instructions of the study procedures during the waiting period. The number of questionnaires returned at Time 2 was 79% (n=100) in PRCI-monitoring, 90% (n=114) in monitoring-control and 82% (n=102) in routine care control. The number of questionnaires returned at Time 3 was 72% (n=92) in PRCI-monitoring, 81% (n=102) in monitoring- control and 73% (n=90) in routine care control group.

Baseline characteristics of the participants are shown in Table I. The three randomised groups were similar on these baseline characteristics except previous use of counselling for infertility, which was more frequent (p=0.009) in the PRCI-monitoring (21.4%) and monitoring-control groups (27%) than in the routine care control group (11.3%). This variable was used as a covariate in subsequent analyses. Participants were also similar on highest education achieved, duration of fertility treatment, child with current partner, child with previous partner, other medical problems, previous experience of miscarriage, abortion, ectopic pregnancy, stillbirth and perinatal death.

Outcomes

All women used the PRCI. Women read the PRCI on average twice a day with a mean of 1.97 (SD: 0.63) and a range from 0.29-4.50. The percentage of women who read PRCI between 1

and twice per day was 47.5%. The percentage of women who read PRCI twice or more a day was 52.5%.

General anxiety

The final model had a random intercept for subject and fixed effects for groups and time with adjustment for the baseline variable previous counselling for infertility and baseline anxiety. For the models for Anxiety and Depression, respectively 4.9% and 4.2% of the studentised residuals were outside the -2 to +2 range. Further, the maximum Restricted Likelihood Distance (ranged 1.0 and 1.3) and the covratio (0.80 to 1.10 and 0.70 to 1.10 for Anxiety and Depression respectively), all indicated no influential observations. The results for HADS-A anxiety indicate a significant main effect of time (F (2, 670)=47.37, p=0.000), but no significant main effect for group (F (2, 373)=2.09, p=0.125) or group by time interaction (F (4, 670)=1.79, p=0.129). The contrast for the significant main effect of time revealed that for all groups the anxiety level was significantly higher during Time 2 (waiting period intervention), than Time 1 (pre-intervention) or Time 3 (post-intervention) (see Figure 3). The mean difference between time 1 versus time 2 was: 1.465 (95%CI 1.098 to 1.832). The mean difference between time 2 versus time 3 was: -1.783 (95%CI -2.175 to -1.392).

General depression

The final model had a random intercept for subject and fixed effects for groups and time with the adjustment for the baseline variables previous counselling for infertility and baseline depression. The results for HADS-D depression indicate a significant effect of time (F (2, 673) =7.04, p=0.001) but no significant main effect for group (F(2, 379) =0.32, p=0.728) or group by time interaction (F(4, 673 =1.38, p=0.241). Contrasts for the significant main effect of time revealed that the depression score was significantly lower at Time 1 (pre-

intervention), compared to Time 2 (waiting period intervention) and Time 3 (post-intervention (see Figure 4). The mean difference between time 1 versus time 2 was 0.514 (95%CI 0.215 to 0.813). The mean difference between time 1 versus time 3 was 0.457 (95%CI 0.148 to 0.766).

Treatment-specific negative and positive emotions

The final model for the daily monitoring data had a random effect for subjects and fixed effects for groups and time with adjustment for vaginal bleeding (spotting). Influential observations for the final models were identified through the distribution of studentised conditional residuals. Only 4.2% of these residuals were outside the -2 to +2 range both in the models for both positive and negative affect. Further, the maximum Restricted Likelihood Distance (1.25 and 1.7) and the covratio (0.90 to 1.15 and 0.85 to 1.10 for positive and negative affect respectively), all indicated no influential observations.

Results for the DRK positive emotions indicated a significant main effect of time ($F(1, 2669)=322.06$, $p=0.000$) and a significant group by time interaction ($F(1, 2652)=16.15$, $p=0.000$) with a non-significant group main effect ($F(1, 285) =1.44$, $p=0.231$). The significant main effect of time showed that the overall slope of positive emotions per day was -0.041 (95% CI -0.046 to -0.037) and the significant group by time interaction showed that the slope of positive emotions per day in the PRCI-monitoring group was higher (0.016, 95% CI 0.008 to 0.024) than in monitoring-control group.

Results for the DRK negative emotions for the two groups indicated a significant main effect of time ($F(1, 2672)=73.93$, $p=0.000$) but no significant main effect of group ($F(1, 292)=1.17$, $p=0.281$) or group by time interaction ($F(1, 2655)=3.38$, $p=0.066$). The significant time effect showed the slope of negative emotions per day was 0.018 (95% CI 0.014 to 0.022). See Figure 5.

Intervention evaluation

Women perceived that the stress of waiting would have been significantly higher without PRCI: mean (SD): 7.04 (2.27), then with PRCI, 6.27 (2.05), PRCI ($t(101)=-7.20$, $p=0.000$). Other aspects of the acceptability, feasibility and perceived helpfulness and benefits of PRCI were all significantly different from the 'no effect' point on the item response scale (all Ps< 0.001). The effect of reading the PRCI was rated as lasting ≤ 20 minutes by 64.4%, mean (SD): 1.62 (1.02), which on average women perceived as long enough, 3.04 (1.41). PRCI was rated as helpful, 3.54 (1.26) and women would use it again, 3.73 (1.56), recommend it to friends, 4.01 (1.34) or recommend it for other medical waiting periods (e.g., genetic testing), 3.66 (1.22). Furthermore the psychological effect of the PRCI was perceived to be in helping to see things more positively, mean (SD): 4.78 (0.93), feeling more positive, 3.40 (1.34), and sustaining coping, 3.05 (1.45). PRCI was less perceived to be a distraction, 2.89 (1.60), and helping in making future plans, 2.36 (1.47).

Practicality was good. PRCI was rated as suitable, mean (SD): 3.97 (1.25), for the waiting period, quick, 4.61 (1.18), and easy, 4.81 (1.07), to use. PRCI fitted in with the daily routine, 4.55 (1.19), and was not perceived to be a hassle to read, 1.89 (1.23). Women could memorise statements, mean (SD): 3.73 (1.31), but thought it was difficult to remember to read the card, 3.08 (1.61).

Treatment outcome

No significant differences were found between groups on clinical pregnancy ($p=0.83$) and clinical pregnancy with heartbeat ($p=0.76$) (see Table II).

Discussion

444 Waiting for the outcome of an IVF/ICSI treatment cycle was stressful with anxiety and
445 depression levels during the waiting period significantly higher than before treatment. Women
446 who used the PRCI intervention during the waiting period of IVF/ICSI reported significantly
447 more positive affect but not significantly less anxiety, depression or negative treatment-
448 specific emotions. Nevertheless, women evaluated the PRCI as acceptable, practical and they
449 perceived a psychological benefit to its use. PRCI had no effect on treatment outcome.
450 Overall, the pattern of results suggests that the main impact of PRCI was to make the stress of
451 the waiting period seem more tolerable rather than in taking away the negative emotions
452 waiting produces. This simple low cost self-help coping intervention can be offered to women
453 to increase positive affect during the waiting period of fertility treatment.
454
455 Waiting for the outcome of treatment was perceived to be stressful and was associated with an
456 increase in general anxiety and depression and negative emotions specific to treatment. These
457 results are consistent with those of numerous studies on ART (Boivin and Takefman, 1995;
458 Boivin and Takefman, 1996; Yong et al. 2000) that show that women appraise the waiting
459 period as a potential threat and as causing related anticipatory negative emotions (e.g.,
460 feelings of worry, tension, nervousness). According to cognitive stress theory, the factors that
461 make waiting periods stressful are the unpredictability and uncontrollability of the outcome
462 (Lazarus and Folkman, 1984). Rumination about the outcome arrests the coping process
463 because coping strategies would differ depending on whether one outcome (pregnant) or the
464 other outcome (not pregnant) was most likely (Lancastle and Boivin , 2008). These results
465 reinforce the need for effective coping interventions that help women manage the strains of
466 medical waiting periods, such as waiting for the pregnancy test in IVF.
467

PRCI produced the effects for which it was designed, namely to help women reinterpret the demands of the waiting period in a more positive way. Women who used PRCI reported significantly more positive emotions (e.g., encouraged, content, confident) during the waiting period than did women assigned to the control group. In addition, patients perceived PRCI to have benefit in helping to manage the stress of fertility treatment, even though PRCI use was not associated with a significant reduction in negative emotional reactions (general or treatment-specific). The generation of challenge emotions (encouraged, confident) is in line with original development data that showed that women using PRCI made more challenge appraisals and perceived the waiting period as more controllable than women using a control intervention (Lancastle, 2006). We have collected further data (to be reported separately) on the effects of PRCI that shows that PRCI is associated with a greater use of positive reappraisal coping compared to the controls groups. Our results support other research showing that positive reappraisal coping is a useful strategy for unpredictable and uncontrollable situations like the medical waiting period (Boivin and Lancastle, 2010). Fredrickson (1998) proposes that positive affect can undo the after-effects of negative emotions. Positive affect may restore autonomic inertness following negative emotional arousal (Fredrickson, 1998). According to Folkman (2011) positive reappraisal and the positive emotions it produces, can allow "psychological respite" during the waiting period, which helps sustain coping during stressful situations. It should be noted too that the PRCI items although originally culled from positive reappraisal measures such as the ways of coping and COPE questionnaire may also tap into other related forms of meaning-based coping (e.g., benefit-finding). Future research needs to consider the extent to which cognitive efforts to redefine the situation and/or derive benefit act synergistically or independently to generate psychological benefits in uncontrollable and unpredictable situations like the waiting period.

We expected that the beneficial effects of PRCI (i.e., generation of positive emotions, perceptions of helpfulness) would reduce the burden of waiting. However, women using PRCI did not report lower day-to-day negative emotions during the waiting period (anxiety, tension, nervousness), or lower general anxiety and depression during and after treatment. Why the intervention only had an effect on positive affect is unclear but there could be a few explanations. There is still an on-going debate about the importance of positive and negative affect, and how they relate to each other (Folkman and Moskowitz, 2000; Folkman 2011). The results of the present study indicate that feeling positive does not necessarily mean one feels less negative. Cognitive reappraisal may play a more definite role in the ability to regulate positive emotions whereas other types of coping (e.g., distraction, acceptance) may be more central in the regulation of negative affect and symptoms of anxiety and depression (Andreotti et al., 2013). The results suggest that interventions may need to comprise multiple modes of coping beside positive reappraisal to help women deal with anxiety and depression during treatment.

Research has demonstrated that positive affect is associated with better physical health and lower risk of mortality, independent of negative affect (Folkman and Moskowitz, 2000; Folkman, 2011). However, in the present study the use of PRCI was not associated with any advantage for treatment outcome. This result is consistent with another study that showed that positive affect was not related to pregnancy rates in fertility treatment (de Klerk et al., 2008) but inconsistent with a study that found that enhanced positive affect was associated with lower probability of failed treatment in IVF (Klonoff-Cohen et al., 2001). Our study differs from the prospective study of Klonoff-Cohen et al. (2001) in the eligibility criteria and the questionnaires and time points used for measuring positive affect. Past reviews and meta-

518 analytic studies on the impact of psychosocial interventions on treatment outcome are
519 inconsistent (Boivin, 2003 ; de Liz and Strauss, 2005; Hammerli et al., 2009). Further our
520 sample size calculation was not based on effect sizes for treatment outcome and therefore may
521 be underpowered for this outcome.
522
523 The results need to be considered in light of the strengths and limitations which should also be
524 considered for future evaluations of the PRCI tool. Feasibility studies had previously been
525 carried out to determine key uncertainties like attrition, recruitment, effect size, acceptability
526 and compliance of the intervention in the present (Lancastle, 2006; Lancastle and Boivin,
527 2008). Attrition was 20% (at Time 2), similar to that observed in previous studies (Lancastle
528 and Boivin, 2008) but was about 30% at Time 3. The use of mixed or multilevel modelling
529 (MLM) allowed analysis of partial response whilst maintaining power (Hoffman and Rovine,
530 2007). However, maximum likelihood estimation has been shown to provide unbiased and
531 efficient estimates only when the data are missing at random (Hoffman and Rovine, 2007).
532 We contend this to be the case but it is possible that attrition was due to some unknown
533 systematic cause. An important aspect of intervention evaluation is to ensure that the
534 intervention is delivered consistently across participants and this is often achieved by
535 manualising the intervention (e.g., manual for lifestyle intervention in infertility, see
536 Ockhuijsen et al., 2012). As a self-administered tool the PRCI comes with a two-page leaflet
537 that describes the rationale for the intervention, including the recommendation that it should
538 be read PRCI twice daily. On average women complied with this recommendation (mean
539 number of times read daily 1.97) but a proportion of women used it less frequently. Lower
540 frequency could reflect that women became less interested in using the tool which could
541 impact on PRCI effects.

The PRCI was designed to help women reinterpret the demands of the waiting period in a more positive way and we used the DRK, a measure of treatment specific reactions, to capture the daily effects of PRCI during the waiting period. However, because daily monitoring itself may have an impact on the reporting of emotions (Cohen et al., 1995) we added a monitoring-control group to disentangle between this methodological artefact and genuine effects of PRCI. We considered this control as a strength of the RCT though this may not be the case. In a parallel study, interviews among women with miscarriage showed that the use of the DRK was affecting emotions, as if the DRK itself was an intervention (unpublished data). If daily monitoring is perceived to be an intervention then the lack of difference observed in the present study between the PRCI and the monitoring-control group could have been due to active effects of monitoring or the possibility that active effects attenuated or obscured effects of the PRCI intervention in unknown ways. Further, the PRCI benefits may be due to an interaction between PRCI and monitoring. The use of a monitoring-control could thus be a weakness of the study because assessment and intervention were confounded. A randomised group of women that used only the PRCI without daily monitoring would provide more insight. We collected such data (n=110) and it would seem that daily monitoring attenuates the effects of PRCI on anxiety and the pregnancy rate. However, only a randomised trial could definitely identify the benefits of PRCI when it is administered on its own.

Another methodological limitation worth considering is the use of the opt-in method to recruit participants. In this method patients indicate a willingness to be included the study (opt-in) instead of the more conventional approach where all patients are enrolled in the trial unless they have indicated a willingness to be excluded (opt-out). Although the opt-out method produces a larger pool of eligible participants at recruitment, ethical committees often do not approve of this method, as was the case in the present RCT, because it requires repeated contact which may be burdensome for participants (Junghans et al., 2005; Treweek et al.,

2010). In an RCT designed to evaluate the effects of the opt-in compared to opt-out recruitment strategies, patients in the opt-in arm were healthier on clinical indicators (e.g., fewer risk factors, symptoms of disease etc) than patients in the opt-out arm, presumably because they could better manage the demands of the study (Junghans et al., 2005; Treweek et al., 2010). In the present study, it is likely that mainly women who were interested in psychological interventions opted-in to participate. Indeed, the overall percentage of past users (19.7%) of infertility counselling in the present sample was higher than previously reported in a British sample (8.5%) (Boivin et al., 1999). It could be that previous use of more in-depth psychological interventions had an impact on study results. Although numbers were too few in the present study to examine this issue fully it warrants consideration in future trials using the opt-in method. Overall readers should consider these limitations as they may affect generalizability.

Although PRCI was not associated with benefit on the psychological questionnaires it was on the intervention evaluation form. Positive evaluations on the intervention form could be due to demand characteristics. However, patient and researcher were not connected in any way, and the medical staff did not have access to any study responses, which makes this possibility unlikely. A discrepancy between outcome measures and intervention evaluations has been reported in previous research (Bird et al., 2011; Emery et al., 2003). In a qualitative study, 15 trial participants and five staff members were interviewed at the end of a trial evaluating a rehabilitation programme that had previously been highly rated by patients (Bird et al., 2011; Emery et al., 2003). Although no scientific evidence was found for the efficacy of the rehabilitation programme, participants and staff members continued to have strong views about the benefit of the intervention. During the interview one of the staff members suggested that "the trial had killed the intervention". Their perspective was that because the pilot phase

had in their opinion been a success, then the process of the RCT must have affected the intervention in such a way as to take away from its benefits. This too may have been an issue for the PRCI trial with, as noted, the addition of monitoring potentially impacting PRCI effects. Bird et al. (2011) recommended that the views and experiences of staff and participants be taken before and after conducting the RCT to evaluate the impact of investigative process on perceptions and we concur with this recommendation. Future research on PRCI could also identify for whom the intervention works best and whether the PRCI could be made more or less effective with change to the item list.

The pattern of results, theoretical, empirical and methodological considerations, all point to the main impact of PRCI as being to make the stress of the waiting period more tolerable than in taking away the negative emotions waiting produces. If PRCI was expensive or difficult to administer one might consider the costs and modest (mainly perceived) benefits of PRCI to argue against a recommendation for the waiting period. However, PRCI is self-administered, comprises a sheet of A4, and can be implemented at a time when patients are not in contact with the medical team or other patients for more interpersonal forms of support. As such we contend that the positive emotions and sense of being helped that PRCI generates are sufficient for it to be offered singly or in combination with other interventions to help women manage the demands of the ART waiting period. Future research should investigate whether PRCI helps to make other medical waiting periods more tolerable.

Authors roles

H.O. designed the trial, monitored data collection for the whole trial, wrote the statistical analysis plan, cleaned and analysed the data, and drafted and revised the paper. A.H. designed the trial, drafted and revised the paper. M.E. cleaned and analysed the data. N.M. initiated the project, designed the trial and revised the draft paper. J.B. designed the trial, designed

intervention and data collection tools, cleaned and analysed the data, and drafted and revised the paper.

Acknowledgements

We thank the participating practices, staff, and patients for their contribution.

Funding

The division Women and Baby of the University Medical Centre Utrecht funded this study.

Conflicts of interest

None declared

References

Andreotti C, Thigpen JE, Dunn MJ, Watson K, Potts J, Reising MM, Robinson KE, Rodriguez EM, Roubinov D, Luecken L *et al*. Cognitive reappraisal and secondary control coping: associations with working memory, positive and negative affect, and symptoms of anxiety/depression. *Anxiety, Stress & Coping* 2013:**26**:20-35.

Benyamini Y, Gozlan M and Kokia E. Variability in the difficulties experienced by women undergoing infertility treatments. *Fertil Steril* 2005:**83**:275-283.

Bird L, Arthur A and Cox K. "Did the trial kill the intervention?" experiences from the development, implementation and evaluation of a complex intervention. *BMC Medical Research Methodology* 2011:**11**:24.

639 Boivin J. A review of psychosocial interventions in infertility. *Soc Sci Med* 2003:**57**:2325-
640 2341.

641 Boivin J. ↲ The Daily Record Keeping Chart: Reliability and validity. Paper presented at the
642 British Psychological Society Special Group in Health Psychology Annual Conference,
643 Southampton, UK, July 1997.

644 Boivin J, Griffiths E and Venetis CA. Emotional distress in infertile women and failure of
645 assisted reproductive technologies: meta-analysis of prospective psychosocial studies. *BMJ*
646 2011:**342**:d223.

647 Boivin J and Lancastle D. Medical waiting periods: imminence, emotions and coping.
648 *Womens Health (Lond Engl)* 2010:**6**:59-69.

649 Boivin J, Scanlan LC and Walker SM. Why are infertile patients not using psychosocial
650 counselling?. *Hum Reprod* 1999:**14**:1384-1391.

651 Boivin J and Takefman JE. Impact of the in-vitro fertilization process on emotional, physical
652 and relational variables. *Hum Reprod* 1996:**11**:903-907.

653 Boivin J and Takefman JE. Stress level across stages of in vitro fertilization in subsequently
654 pregnant and nonpregnant women. *Fertil Steril* 1995:**64**:802-810.

655 Campbell M, Fitzpatrick R, Haines A, Kinmonth AL, Sandercock P, Spiegelhalter D and
656 Tyrer P. Framework for design and evaluation of complex interventions to improve health.
657 *BMJ* 2000:**321**:694-696.

658 Cohen S, Kessler RC and Gordon LU. *Measuring stress : a guide for health and social*
659 *scientists.* 1995. Oxford University Press, New York.

660 Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M and Medical Research
661 Council Guidance. Developing and evaluating complex interventions: the new Medical
662 Research Council guidance. *BMJ* 2008:**337**:a1655.

663 de Klerk C, Hunfeld JA, Heijnen EM, Eijkemans MJ, Fauser BC, Passchier J and Macklon
664 NS. Low negative affect prior to treatment is associated with a decreased chance of live birth
665 from a first IVF cycle. *Hum Reprod* 2008:**23**:112-116.

666 de Klerk C, Hunfeld JA, Duivenvoorden HJ, den Outer MA, Fauser BC, Passchier J and
667 Macklon NS. Effectiveness of a psychosocial counselling intervention for first-time IVF
668 couples: a randomized controlled trial. *Hum Reprod* 2005:**20**:1333-1338.

669 de Liz TM and Strauss B. Differential efficacy of group and individual/couple psychotherapy
670 with infertile patients. *Hum Reprod* 2005:**20**:1324-1332.

671 De Sutter P, Bontinck J, Schutysers V, Van der Elst J, Gerris J and Dhont M. First-trimester
672 bleeding and pregnancy outcome in singletons after assisted reproduction. *Hum Reprod*
673 2006:**21**:1907-1911.

674 Emery M, Beran MD, Darwiche J, Oppizzi L, Joris V, Capel R, Guex P and Germond M.
675 Results from a prospective, randomized, controlled study evaluating the acceptability and
676 effects of routine pre-IVF counselling. *Hum Reprod* 2003:**18**:2647-2653.

677 Eugster A and Vingerhoets AJ. Psychological aspects of in vitro fertilization: a review. *Soc*
678 *Sci Med* 1999:**48**:575-589.

679 Folkman S and Lazarus RS. The relationship between coping and emotion: implications for
680 theory and research. *Soc Sci Med* 1988:**26**:309-317.

681 Folkman S and Lazarus RS. If it changes it must be a process: study of emotion and coping
682 during three stages of a college examination. *J Pers Soc Psychol* 1985:**48**:150-170.

683 Folkman S and Moskowitz JT. Positive affect and the other side of coping. *Am Psychol*
684 2000:**55**:647-654.

685 Folkman S. Positive psychological states and coping with severe stress. *Soc Sci Med*
686 1997:45:1207-1221.

687 Folkman S. *The Oxford handbook of stress, health, and coping*. 2011. Oxford University
688 Press, Oxford; New York.

689 Fredrickson BL. What good are positive emotions?. *Review of general psychology: journal of*
690 *Division 1, of the American Psychological Association* 1998:**2**:300.

691 Hammerli K, Znoj H and Barth J. The efficacy of psychological interventions for infertile
692 patients: a meta-analysis examining mental health and pregnancy rate. *Hum Reprod Update*
693 2009:**15**:279-295.

694 Hoffman L and Rovine MJ. Multilevel models for the experimental psychologist: foundations
695 and illustrative examples. *Behav Res Methods* 2007:**39**:101-117.

696 Junghans C, Feder G, Hemingway H, Timmis A and Jones M. Recruiting patients to medical
697 research: double blind randomised trial of "opt-in" versus "opt-out" strategies. *BMJ*
698 2005:**331**:940.

699 Lancastle, D. Reasons to Be Cheerful: Part I, II, III : Dispositional Optimism, Positive
700 Reappraisal Coping and Positive (Re)appraisals of the Situation : Effects on Emotional Well-

being and Physical Outcomes. Cardiff University 2006: n.p.: ProQuest, UMI Dissertations Publishing.

Lancastle D and Boivin J. A feasibility study of a brief coping intervention (PRCI) for the waiting period before a pregnancy test during fertility treatment. *Hum Reprod* 2008:**23**:2299-2307.

Lazarus RS, Folkman S: *Stress, appraisal, and coping*:. 1984. Springer Pub. Co, New York.

Matthiesen SM, Frederiksen Y, Ingerslev HJ and Zachariae R. Stress, distress and outcome of assisted reproductive technology (ART): a meta-analysis. *Hum Reprod* 2011:**26**:2763-2776.

Merari D, Feldberg D, Elizur A, Goldman J and Modan B. Psychological and hormonal changes in the course of in vitro fertilization. *J Assist Reprod Genet* 1992:**9**:161-169.

Ockhuijsen HDL, Gamel CJ, van den Hoogen A and Macklon NS. Integrating preconceptional care into an IVF programme. *J Adv Nurs* 2012:**68**:1156-1165.

Phelps C, Bennett P, Hood K, Brain K and Murray A. A self-help coping intervention can reduce anxiety and avoidant health behaviours whilst waiting for cancer genetic risk information: results of a phase III randomised trial. *Psychooncology* 2012:**22**:836-844..

Polit DF and Beck CT. *Nursing research : generating and assessing evidence for nursing practice* 2008: Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins,796 p.

Polit DF and Hungler BP. *Nursing research : principles and methods* 1999: Philadelphia, New York, Baltimor: Lippincott Company,757 p.

720 Provoost V, Pennings G, De Sutter P, Gerris J, Van de Velde A and Dhont M. Patients'
721 conceptualization of cryopreserved embryos used in their fertility treatment. *Hum Reprod*
722 2010:**25**:705-713.

723 Svanberg AS, Boivin J, Hjelmstedt A, Bergh LA, Collins A and Bergh T. The impact of
724 frozen embryos on emotional reactions during in vitro fertilization. *Acta Obstet Gynecol*
725 *Scand* 2001:**80**:1110-1114.

726 Tedlie Moskowitz J, Folkman S, Collette L and Vittinghoff E. Coping and mood during aids-
727 related caregiving and bereavement. *Annals of Behavioral Medicine* 1996:**18**:49-57.

728 Treweek S, Pitkethly M, Cook J, Kjeldstrom M, Taskila T, Johansen M, Sullivan F, Wilson S,
729 Jackson C, Jones R *et al*. Strategies to improve recruitment to randomised controlled trials.
730 *Cochrane Database Syst Rev* 2010:**4**:MR000013.

731 Van Dongen AJ, Kremer JA, Van Sluisveld N, Verhaak CM and Nelen WL. Feasibility of
732 screening patients for emotional risk factors before in vitro fertilization in daily clinical
733 practice: a process evaluation. *Hum Reprod* 2012:**27**:3493-3501.

734 Velten E,Jr. A laboratory task for induction of mood states. Behav Res Ther 1968:6:473-482.
735 Verhaak CM, Lintsen AM, Evers AW and Braat DD. Who is at risk of emotional problems
736 and how do you know? Screening of women going for IVF treatment. *Hum Reprod*
737 2010:**25**:1234-1240.

738 Yong P, Martin C and Thong J. A comparison of psychological functioning in women at
739 different stages of in vitro fertilization treatment using the mean affect adjective check list. *J*
740 *Assist Reprod Genet* 2000:**17**:553-556.

741 Zegers-Hochschild F, Adamson GD, de Mouzon J, Ishihara O, Mansour R, Nygren K,
742 Sullivan E and van der Poel S. The International Committee for Monitoring Assisted
743 Reproductive Technology (ICMART) and the World Health Organization (WHO) Revised
744 Glossary on ART Terminology, 2009. *Human Reproduction* 2009:**24**:2683-2687.

745 Zigmond AS and Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*
746 1983:**67**:361-370.