Human Reproduction Update, Vol.15, No.3 pp. 279–295, 2009
Advanced Access publication on February 5, 2009 doi:10.1093/humupd/dmp002

human reproduction update

The efficacy of psychological interventions for infertile patients: a meta-analysis examining mental health and pregnancy rate

Katja Hämmerli[1,3], Hansjörg Znoj[1], and Jürgen Barth[2]

[1]Institute of Psychology, Department of Clinical Psychology and Psychotherapy, University of Bern, Switzerland [2]Institute of Social und Preventive Medicine (ISPM), Division of Social and Behavioural Health Research, University of Bern, Switzerland

[3]Correspondence address. E-mail: katja.haemmerli@ptp.unibe.ch

TABLE OF CONTENTS

BACKGROUND: Psychological interventions for infertile patients seek to improve mental health and increase pregnancy rates. The aim of the present meta-analysis was to examine if psychological interventions improve mental health and pregnancy rate among infertile patients. Thus, controlled studies were pooled investigating psychological interventions following the introduction of assisted reproductive treatments (ART).

METHODS: The databases of Medline, PsycINFO, PSYNDEX, Web of Science and the Cochrane Library were searched to identify relevant articles published between 1978 and 2007 (384 articles). Included were prospective intervention studies on infertile patients (women and men) receiving psychological interventions independent of actual medical treatment. The outcome measures were mental health and pregnancy rate. A total of 21 controlled studies were ultimately included in a meta-analysis comparing the efficacy of psychological interventions. Effect sizes (ES) were calculated for psychological measures and risk ratios (RR) for pregnancy rate.

RESULTS: The findings from controlled studies indicated no significant effect for psychological interventions regarding mental health (depression: ES 0.02, 99% CI: −0.19, 0.24; anxiety: ES 0.16, 99% CI: −0.10, 0.42; mental distress: ES 0.08, 99% CI: −0.10, 0.51). Nevertheless, there was evidence for the positive impact of psychological interventions on pregnancy rates (RR 1.42, 99% CI: 1.02, 1.96). Concerning pregnancy rates, significant effects for psychological interventions were only found for couples not receiving ART.

CONCLUSIONS: Despite the absence of clinical effects on mental health measures, psychological interventions were found to improve some patients' chances of becoming pregnant. Psychological interventions represent an attractive treatment option, in particular, for infertile patients who are not receiving medical treatment.

Key words: assisted reproductive treatment / infertility / meta-analysis / psychological intervention / pregnancy

Introduction

Couples often describe the experience of infertility as a critical, significant life event bearing emotional challenges (Menning, 1980; Freeman *et al.*, 1985; Dunkel-Schetter and Lobel, 1991). Nevertheless, on balance, infertile patients do not differ from the general population with respect to short-term (Wright *et al.*, 1989; Dunkel-Schetter and Lobel, 1991; Leiblum and Greenfield, 1997; Covington and Burns, 2006) or long-term (Strauss *et al.*, 2004) levels of mental distress, anxiety and depression.

In addition to the evidence of encouraging long-term adaptation processes among infertile couples, there is clear empirical evidence that assisted reproductive treatments (ART) have a negative short-term influence on the mental distress levels of such couples. In several studies, infertile patients undergoing ART reported high levels of depressive symptoms, anxiety and distress (Greil, 1997; Brkovich and Fisher, 1998; Eugster and Vingerhoets, 1999; Chen *et al*., 2004). Higher levels of anxiety and depression were also found among infertile women not receiving ART when compared with a representative sample of the German population (Wischmann *et al*., 2001b).

In some studies, high levels of depressive symptoms, anxiety and distress have been associated with reduced chances of becoming pregnant during ART (Demyttenaere *et al*., 1992, 1998; Thiering *et al*., 1993; Facchinetti *et al*., 1997; Klonoff-Cohen *et al*., 2001; Smeenk *et al*., 2001). Other authors have failed to find a relationship between women's mental distress and their chances of becoming pregnant during ART (Visser *et al*., 1994; Boivin and Takefman, 1995; Harlow *et al*., 1996; Slade *et al*., 1997). Systematic reviews (Eugster and Vingerhoets, 1999; Klonoff-Cohen, 2005; Homan *et al*., 2007) have summarized these controversial findings and concluded that psychosocial factors like psychosocial distress, ineffective coping strategies, anxiety and depression may possibly lower one's chances of becoming pregnant.

Two major goals of psychological interventions for infertile patients are to improve their mental health and increase their pregnancy rate. Two previously published reviews sought to examine the efficacy of such psychological interventions with respect to the mental health and pregnancy rate of infertile patients.

In a first narrative review, Boivin (2003) examined whether specific psychological interventions are more efficacious than usual care. According to her review, mixed results were obtained for the efficacy of psychological interventions with respect to anxiety and depression among infertile patients. Positive study results were found more frequently in connection with anxiety (8 of 13 analyses, 61.5%) than in connection with depressive symptoms (5 of 13 analyses, 38.4%). No clear effect was found for psychological interventions with respect to interpersonal functioning (3 of 11 analyses, 27.3%); however, infertility-specific stress was reduced in all studies (six of six analyses, 100%) and target behaviour (e.g. sexual behaviour) was also modified in 10 of 10 analyses (100%). No clear efficacy for psychological interventions was reported for pregnancy rates following treatment; three of eight analyses reported an increased pregnancy rate 6–18 months after the psychological intervention.

In a second review, de Liz and Strauss (2005) conducted a meta-analysis of the comparative efficacy of psychological interventions in group settings versus those in individual or couples settings. The studies they included assessed anxiety ($N = 10$), depressive symptoms ($N = 10$) and pregnancy rate ($N = 16$). It is important to note that pre–post effect sizes (ES) were calculated for psychological measures without taking into account the study design, i.e. no comparisons to control groups were reported by the authors. With respect to anxiety, their results pointed to the efficacy of psychotherapeutic strategies labelled both as individual or couples psychotherapy (significant ES 0.17, 95% CI: 0.05, 0.29) and those labelled as group therapy (significant ES 0.36, 95% CI: 0.24, 0.48) in a pre–post comparison. They also report of a weak pre–post intervention effect on depressive symptoms for individual or couples psychotherapy (ES 0.12, 95% CI: 0.002, 0.24) and group therapy (ES 0.19, 95% CI: 0.07, 0.31). However, the review's most interesting result was its report of a higher conception rate among patients following a psychotherapeutic intervention. The mean pregnancy rate for patients who received psychotherapy preceding or accompanying their treatment for infertility was 45% (18 studies), whereas only 14% of the patients in control groups (six studies) became pregnant.

These two initial reviews came to divergent conclusions regarding the resulting pregnancy rate; and, in the case of de Liz and Strauss (2005), this was a very prominent result of the study. While de Liz and Strauss (2005) reported an enhanced pregnancy rate from controlled and uncontrolled studies, Boivin (2003) came to a more cautious interpretation from eight controlled studies of higher methodological quality. In order to arrive at a valid conclusion, it is essential to compare the resultant pregnancy rates solely from controlled studies. Otherwise, researchers risk ignoring factors contributing to the pregnancy rate that should have been controlled for. Therefore, it is possible that de Liz and Strauss' study overestimates the efficacy of psychological interventions for infertile patients in regard to pregnancy rate.

The present meta-analysis sought to provide more definitive answers regarding the efficacy of psychological interventions for infertile patients by limiting its analysis to controlled investigations and by integrating those relevant studies published recently.

The following research questions were examined:

(i) Do psychological interventions improve mental health (anxiety, depression, mental distress, interpersonal functioning and infertility-specific stress) in patients with infertility?
(ii) Are psychological interventions effective in increasing the pregnancy rate among infertile couples?
(iii) Do study and patient characteristics (sex, duration of intervention, ART and randomization) alter the efficacy of the psychological interventions studied?

Methods

Inclusion and exclusion criteria

The inclusion criteria for the studies were: (i) study participants had to be infertile women and men independent of actual medical treatment; (ii) prospective study designs; (iii) participants must have received a psychological intervention (e.g. counselling, cognitive-behavioural therapy, educational interventions, relaxation, psychodynamic/-analytic interventions); and (iv) the study had to report on one outcome measure at minimum (mental health, interpersonal functioning, infertility-specific stress or pregnancy rate).

The included studies drew from both published and unpublished sources, and the literature search was limited to the timeframe from 1978 to 2007. The year 1978 was selected as a lower limit since that year marked the first time a child was born as a result of *in vitro* fertilization (IVF), greatly altering medical treatment of infertility from then on. Owing to the introduction of such medical treatments, the period prior to 1978 simply is not comparable with the period following. Finally, studies of any language or cultural background were considered eligible for inclusion. Case reports, unsystematic narratives, expert opinions, magazines, newspaper articles and commentaries were excluded.

Design

For the meta-analysis, studies were included that employed a control group design independent of their type of allocation (randomized or non-randomized). These studies were used to compare post-intervention efficacy of the psychological intervention.

Participants and definition of infertility

The study participants were women and men suffering from infertility, independent of the actual medical treatment used to treat their infertility. Different definitions and classifications of infertility exist, and stem either from the World Health Organization (WHO) or organizations like the European Society of Human Reproduction and Embryology (ESHRE) or from the authors of primary studies themselves. For clinical purposes, the gold standard definition of infertility is 'the inability of a couple to achieve conception or to bring a pregnancy to term after a year of regular, unprotected sexual intercourse' (WHO, 2002). Nevertheless, a cut-off value of 2 years is used in many epidemiological studies (WHO, 1975). In addition to these dichotomous classifications, there are also graded classification systems of infertility in use, with grading ranging from fertile to infertile based on the duration of one's unfulfilled wish for a child and clinical characteristics (Gnoth *et al*., 2005; Habbema *et al*., 2004). Since there is no clear, accepted definition utilized by everyone, the present meta-analysis included any studies using a sample labelled as infertile according to any of the above-mentioned definitions.

Interventions

For the purposes of the present meta-analysis, a psychological intervention was defined as a face-to-face intervention: (i) designed to influence psychological functioning; (ii) based on a psychological theory and (iii) incorporating psychological strategies through interaction. The psychological interventions could be provided in a variety of settings (i.e. individual, couple or group; inpatient or outpatient).

Control group conditions

The control group participants did not receive a psychological intervention. They were either on waiting lists or received routine care. The meta-analysis also included two studies that reported of patients who declined the intervention, as long as such patients constituted $<50\%$ of the total sample of the control group (Ellenberg and Koren, 1982; Strauss *et al*., 2002).

Outcome measures

The outcome measures were psychological dimensions as well as the resultant pregnancy rate. The psychological dimensions comprised depressive symptoms, anxiety, mental distress, interpersonal functioning and infertility-specific stress. These dimensions were all assessed through the use of self-report questionnaires. Pregnancy rate was defined as evidence of pregnancy according to clinical or ultrasound parameters (ultrasound visualization of a gestational sac; Zegers-Hochschild *et al*., 2006). The resultant pregnancy rate was assessed either by patients' self-reports or according to the reports of their clinicians.

Literature search and data sources

A systematic approach was used to identify relevant studies. The following databases were searched for relevant studies published between 1978 and 2007: MEDLINE (U.S. National Library of Medicine, 1978 to April 2007), PsycINFO (American Psychological Association, 1978 to January–March 2007), PSYNDEX (German database of the Center for Psychological Information and Documentation at the University of Trier, Germany 1978 to January–March 2007), Web of Science (Social Sciences Citation Index, 1978 to April 2007) and the Cochrane Library (1978 to Issue 1, 2007). When performing the search, two primary concepts were combined with 'and'. The two primary search concepts were: (i) 'infertil*', 'fertility disorder/treatment/problems', 'sterility', 'IVF', 'ICSI', 'involuntary childlessness', 'ET', 'assisted reproduction' *and* (ii) 'psychotherap*', 'CBT', 'psychological intervention', 'psychoeducation', 'hypnosis', 'autogenic training', 'behavioural therapy' (see the Supplementary Appendix for detailed information on the literature search). All results were downloaded and stored in the reference database program EndNote 10. The database search resulted in 384 references.

A total of eight reviews were found as a result of this initial search. Next, the eight reviews were manually checked for further study citations. In addition, the congress abstracts of ESHRE (European Society of Human Reproduction, 2002 to 2006) and ASRM (American Society for Reproductive Medicine, 2002 to 2006) were searched for unpublished studies, and the authors of these studies were contacted. In sum, five authors of controlled studies were contacted for additional information: all of them responded. As a result of the manual search, 13 additional references were included in the meta-analysis.

Study selection and data extraction

The initial literature search of databases yielded 384 references. Next, 307 references were excluded based on their titles or abstracts. In an additional step, 49 references were excluded on the basis of their contents. In the end, 21 studies (culled from the database search plus from the manual search) published in 26 papers were included in the meta-analysis. A total of 356 references were ultimately excluded and coded according to their reason for exclusion (see Supplementary Appendix). The respective reasons for exclusion were: (i) the study was not an empirical investigation ($n = 253$); (ii) the study did not report on a psychological intervention ($n = 77$); (iii) due to the characteristics of the study's sample (no infertile persons, $n = 14$); (iv) excluded as review ($n = 8$) and (v) due to the absence of an evaluation of the psychological intervention ($n = 4$).

In order to conduct a reliability analysis of the selection process (i.e. study inclusion or exclusion), the first author and another trained person independently rated 80 publications on the basis of their title and abstract. Their percentage of agreement and the inter-ratter reliabilities (kappa) were as follows: study excluded = 93% (kappa = 0.84); study included based on title and/or abstract = 99% (0.94); excluded as review = 99% (0.66) and unclear = 93% (NA). The percentage agreement (inter-rater reliabilities) for the exclusion criteria were as follows: no psychological intervention = 96% (0.89); no evaluation of the intervention = 99% (NA); incorrect sample = 99% (0.66); non-empirical report or case reports = 96% (0.92). These numbers indicate excellent reliability of study selection.

The present meta-analysis included 21 studies that utilized a control group. An additional 14 studies were found that only reported results of an uncontrolled design; they were excluded from the meta-analysis. Finally, six studies with a controlled design were treated as uncontrolled studies and excluded from the meta-analysis due to one of the following reasons: no face-to-face intervention (Cousineau *et al*., 2006), dropout of control group (Clark *et al*., 1995, 1998; Galletly *et al*., 1996b), fertile control group (O'Moore *et al*., 1983) or insufficient data (Takefman *et al*., 1990; Melamed *et al*., 2005).

Data extraction

The first author and one other trained person independently rated all data of the included studies. Both reviewers coded each study in a paper/pencil codebook. Following this initial coding, differences between the two

reviewers were solved in discussion, giving rise to a final joint coding. The calculation of ES and the calculation of standard errors of effect measures were performed through a double data extraction procedure (K.H. and J.B.).

Effect size calculation and data analysis

All the outcome measures were assessed post-intervention or at follow-up (FU) (ranging from 1 to 12 months). ES for interval data were calculated through comparisons between groups independent of their baseline value. Only one ES was calculated per individual study. If data from three groups were available stemming from one study (two different intervention groups plus one control group), one ES was calculated for the entire study through a collective comparison of the effects registered by its treatment groups versus the control conditions (McQueeney *et al*., 1997; Domar *et al*., 2000a, b; Wischmann *et al*., 2001a, b, 2002; Strauss *et al*., 2002; Emery *et al*., 2003, 2006). If data from female and male participants were available, they were included separately in the meta-analysis and used for subgroup analysis.

ES for interval data were calculated from mean and standard deviation using Wilson's (2001) ES calculator. In one study (Tuschen-Caffier *et al*., 1999), where solely median data were reported, the ES was calculated using the approach developed by Hozo *et al*. (2005). An ES of $\geq$0.20 to 0.50 indicates a low effect; $\geq$0.50 to 0.80 indicates a medium effect and $\geq$0.80 indicates a large effect (Cohen, 1977) between groups. ES $>$ 0 indicate a beneficial effect for the given psychological intervention. The standard error of ES was separately computed in an Excel sheet according to the formula provided by Lipsey and Wilson (2001). ES differences were computed according to Altman and Bland (2003).

Data on the number of pregnancies following the intervention were compared with the number of pregnancies in the control group using relative risks. Since missing data are highly relevant when measuring the efficacy of interventions, the pregnancy rate was calculated using an intention to treat (ITT) analysis or, if the data were not sufficient, from FU data only. According to the ITT model, patients were classified as childless if they were not reached at FU. The FU model was restricted to information stemming from subjects with FU information available. Relative risks of the pregnancy rate were calculated (Rosenthal *et al*., 2000), i.e. a relative risk larger than 1 indicates a higher pregnancy rate for the intervention group versus usual care and vice versa.

Data analysis was carried out using Review Manager 5.0 (2007). The main analysis focused on outcome measures through a comparison of intervention and control groups. All subgroup analyses followed prespecified hypotheses of confounders of efficacy. For the pooling of interval data, the standardized mean procedure was chosen since the outcome measures differed between studies. For the pooling of the relative risk, the Mantel–Haenszel approach (Hauck, 1989) was used. A random effect model for pooling the studies was employed in all outcomes due to the anticipated heterogeneity of the primary studies. The 99% CI was used since multiple hypotheses were tested. The CIs represent 99% ranges, which indicate a statistically significant effect when zero (0) values are excluded from the ES measures or values of 1 are excluded from the relative risks.

Heterogeneity between the studies was assessed by examining forest plots of trials, by calculating a chi-square heterogeneity test and through I^2 statistics. The chi-squared value is used to test for statistically significant heterogeneity between trials and indicates heterogeneity if statistical significance is found. In addition, higher I^2 values indicate greater variability between trials than would be expected due to chance alone (range 0–100%; Higgins *et al*., 2003). Higgins *et al*. (2003) propose as heterogeneity indicators I^2 values of 25% for low heterogeneity, 50% for moderate heterogeneity and 75% for high heterogeneity. As publication bias might be present, data were analysed from each outcome in funnel plots in order to spot unexpected study results. The results of the funnel plots are available via the Internet.

Results

Description of studies

A total of 21 studies were included in the meta-analysis of controlled studies (Table I; the included studies are marked in the reference list). Exactly 1420 persons were assigned to the intervention group and 3342 persons were assigned to the control group. Of the total number of studies, 11 were carried out in Europe (three in Germany, two in Italy and one each in the UK, the Netherlands, Switzerland, Israel, the Czech Republic and Denmark), 5 were from the US, 3 were from China and 2 were from Canada. The majority of the studies were published in English ($n = 19$), whereas one study was written in German and another in Chinese. Further, 10 of the studies reported on patients receiving ART (IVF/intracytoplasmic sperm injection: ICSI) for infertility, whereas 8 of the studies investigated patients not receiving IVF/ICSI (i.e. receiving other medical treatments like intrauterine sperm insemination). Finally, three of the studies reported on patients who received mixed treatments. In the majority of the studies, patients were referred by their general practitioner or by fertility clinics. In some of the studies, patients were recruited by newspaper advertisements, from adoption waiting lists or from psychiatric services. The mean duration of infertility was 3.8 years (1.5–5.9). The mean age of the intervention group participants was 32.7 (27–36.5), whereas the mean age of the control group participants was 32.9 (27–38.5). A total of seven studies included women only; seven studies included men and women and seven studies treated couples only. Randomized allocation was used in 12 of the studies, whereas 9 of the studies used non-randomized allocation.

The following psychosocial outcomes were reported (number of studies): depression (12), anxiety (12), mental distress (8), interpersonal functioning (5) and infertility-specific stress (5). Pregnancy rates were reported in 14 of the studies. Most of the studies assessed other dimensions as well (e.g. self-efficacy, implantation rate, intensity of the wish for a child) not covered by the dimensions listed above (14). The time point of assessment following the intervention varied strongly from 30 min on up to 3 years. Most of the studies measured outcomes between 4 weeks and 6 months after the psychological intervention.

The intervention strategies employed included counselling (Connolly *et al*., 1993; Wischmann *et al*., 2001a, b, 2002; McNaughton-Cassill *et al*., 2002; Strauss *et al*., 2002; Emery *et al*., 2003, 2006; De Klerk *et al*., 2005; Zhen *et al*., 2005), cognitive-behavioural therapies (Stewart *et al*., 1992; Liswood, 1995; Domar *et al*., 2000a, b; Facchinetti *et al*., 2004; Tarabusi *et al*., 2004), education (McQueeney *et al*., 1997; Tuschen-Caffier *et al*., 1999; Shu-Hsin, 2003; Chan *et al*., 2006), mind/body orientated relaxation (Rezabek *et al*., 2003; Levitas *et al*., 2006), psychodynamic/-analytic (Ellenberg and Koren, 1982; Sarrel and DeCherney, 1985) and mixed interventions (Schmidt *et al*., 2005). The total duration of the interventions varied between 1–5 h (8), 6–12 h (8), 13–25 h (3) and $>$25 h (1). The number of sessions was comparable with the total duration: 1–5 sessions (8), 6–12 sessions (10) and 13–32 sessions (1). In 11 of the studies, patients in the control group did not

Table I Controlled studies included in the meta-analysis

Reference, country	Sample	Methods	Setting and intervention	Measures	Main results	Quality indicators
Study	(1) Size and sex; (2) cause of infertility; (3) infertility duration; (4) number of IVF/ICSI	(1) Design; (2) time of measurement; (3) type and intervention of comparison group; (4) dropouts	Medical treatment, type, format, duration, intensity per week (total s), total time)	(1) anxiety; (2) depression; (3) mental health; (4) interpersonal functioning; (5) infertility-specific stress; (6) pregnancy; (7) other measures		(1) Standardized measures of psych. outcomes; (2) randomization; (3) blinding; (4) IG comparable to CG; (5) comparable care (characteristics of sample); (6) dropouts before allocation; (7) dropouts during study $\leq$20%; (8) $\leq$20% difference of dropouts in IG and CG; (9) inclusion criteria reported
Study No. 1, Chan *et al.* (2006), China	(1) IG = 69 F, CG = 115 F; (2) tubal: 25 (IG), 33 (CG), male factor: 23, 51, endometriosis: 7, 17, unexplained: 5, 8, mixed: 9, 6; (3) 5 y; (4) 0	(1) Randomized controlled study; (2) T0: baseline, T1: 2 m, T2: 3 m; (3) like IG, no; (4) 43 F	IVF/ICSI, psychoeducational group counselling, group/woman, 4 w, 1 s for 3h (4), total 12 h	(1) STAI; (2) no; (3) no; (4) no; (5) no; (6) yes; (7) childbearing importance index, no. of embryos replaced, implantation rate, multiple pregnancy rate	Sign. less state anxiety after the intervention; no association with pregnancy rate was detected	(1) Both; (2) yes; (3) no; (4) yes; (5) yes; (6) >40%; (7) yes; (8) no; (9) yes
Study No. 2, Connolly *et al.* (1993), UK	(1) IG = 37 C, CG = 45 C; (2) 101 C: organic factor, 26 C male factor, 57 C female factor, 18 C both; (3) M = 3.5 y; (4) 0	(1) Randomized controlled study; (2) T0: baseline, T1: for begin of treatment cycle (6 w), T2: at the end of first treatment cycle (3 m); (3) like IG, info and RC; (4) 70 C	IVF/ICSI, non-directive counselling and information, individual/couple, 3 w, 1 s for 1 h (3), total 3 h	(1) STAI; (2) POMS; (3) GHQ, POMS, SES; (4) no; (5) SI; (6) no; (7) course evaluation	Intervention compared with CG did not lead to any enhanced reduction in levels of anxiety and depression	(1) Yes; (2) yes; (3) no; (4) yes; (5) yes; (6) $\leq$20%; (7) no; (8) yes; (9) yes
Study No. 3, De Klerk *et al.* (2005), the Netherlands	(1) IG = 22 C, CG = 22 C; (2) IG: 8 female factor, 8 male factor, 1 both, 4 unclear, KG: 3 female factor, 8 male factor, 2 both, 6 unclear; (3) IG: 4.0 (1.7), CG: 4.3 (3.6); (4) 0	(1) Randomized controlled study; (2) T0: before treatment, T1; after treatment; (3) like IG, RC; (4) 40 C	IVF/ICSI, psychosocial counselling, individual/couple, 4 w, 1 s for 1 h (3), total 3 h	(1) HADS; (2) HADS; (3) HADS, DRK; (4) no; (5) no; (6) yes; (7) no	No sign. differences were found; counselling did not help the couples	(1) Yes; (2) yes; (3) no; (4) yes; (5) yes; (6) >40%; (7) no; (8) yes; (9) yes
Study No. 4, Domar *et al.* (2000a, b), USA	(1) IG = 47 F + 48 F, CG = 25 F; (2) n. r.; (3) IG1 = 1.55 (0.29, N: 56) IG2 = 1.49 (0.34, N: 65) CG = 1.45 (0.28, N: 63); (4) IG1: 8/14%, IG2: 13/20%, CG: 8/13%	(1) Randomized controlled study; (2) T0: baseline, T1: 6 m, T2: 12 m; (3) like IG, RC; (4) 64 F	No IVF/ICSI, cognitive behavioural and support, group/woman, 10 w, 1 s for 2 h (10), total 20 h	(1) STAI; (2) BDI, HRDS (fu); (3) POMS, RSES; (4) MDS; (5) no; (6) yes; (7) psychiatric interviews	Positive effect of intervention on psychological outcomes and pregnancy	(1) Yes; (2) yes; (3) yes; (4) yes; (5) yes; (6) $\leq$20%; (7) no; (8) yes; (9) yes

Continued

Table I *Continued*

Reference, country	Sample	Methods	Setting and intervention	Measures	Main results	Quality indicators
Study No. 5, Ellenberg and Koren (1982), USA	(1) IG = 6 F, CG = 7 F; (2) primary and secondary unexplained infertility; (3) 2–11 y; (4) n. r.	(1) Controlled study; (2) T: after 3 y; (3) refused counselling, no; (4) 5 F	No IVF/ICSI, psychoanalytic and antidepressive, individual/woman, 64–121 w, 1 s for 45 min (12–64), total 9–48 h	(1) No; (2) no; (3) no; (4) no; (5) no; (6) yes; (7) no	Sign. more patients were pregnant in the intervention group compared with the control group	(1) n.r.; (2) no; (3) no; (4) yes; (5) yes; (6) unclear; (7) no; (8) yes; (9) yes
Study No. 6, Emery *et al.* (2003, 2006), Switzerland	(1) IG = 86 S, CG = 70 S; (2) 50% male and 50% female factor; (3) 3.8 ± 2.1 y; (4) 0	(1) Randomized controlled study; (2) T0: for intervention and start of IVF, T1: 6 w after IVF, T2: 1 y after IVF; (3) like IG, only info; (4) 14 S	IVF/ICSI, psychological counselling, individual/couple, total 1–1.5 h	(1) STAI; (2) BDI; (3) no; (4) no; (5) no; (6) yes; (7) assessments of counselling	No sign. effect of counselling on pregnancy rate, anxiety and depression scores.	(1) Yes; (2) yes; (3) no; (4) yes; (5) yes; (6) ≤20%; (7) unclear; (8) unclear; (9) yes
Study No 7, Facchinetti *et al.* (2004), Italy	(1) IG = 26 S, CG = 19 S; (2) IG: 2 unexplained, 5 mechanical, 19 both partners, KG: 4 unexplained, 4 mechanical, 11 both; (3) IG: 2.5 ± 1.3 y (1–4), KG: 3.8 ± 3.0 y (2–19); (4) IG = 21 and CG = 9 at least one attempt	(1) Controlled study; (2) T0: baseline, T1: 4 m; (3) negative or no changes in heart rate, no; (4) 45 S	IVF/ICSI, CBT intervention, group/couple, 4 m, 1 s for 1 h (12), total 12 h	(1) No; (2) no; (3) no; (4) no; (5) no; (6) no; (7) systolic blood pressure, heart rate, plasma cortisol, stroop colour-word test	Intervention was useful for decreasing the level of distress	(1) n.r.; (2) no; (3) no; (4) no; (5) yes; (6) ≤20%; (7) unclear; (8) unclear; (9) yes
Study No. 8, Levitas *et al.* (2006), Israel	(1) IG = 89 F, CG = 96 F; (2) IG: 46.9% primary infertility, 44.9% male factor, 14.3% pelvic and tubal, 18.4% unexplained, CG: 74.2% primary infertility, 44.3% male factor, 16.5% pelvic and tubal, 10.3% unexplained; (3) IG: 4.7 y (SD = 3.1), CG: 7.4 y (SD = 4.3); (4) n. r.	(1) Controlled study; (2) T: after intervention and result of ET; (3) like IG, no; (4) 0	IVF/ICSI, hypnosis, individual/woman, during ET	(1) No; (2) no; (3) no; (4) no; (5) no; (6) yes; (7) implantation rate	Hypnosis during ET sign. improved the IVF/ET cycle outcome in terms of increased implantation and pregnancy rate	(1) n.r.; (2) no; (3) no; (4) yes; (5) yes; (6) unclear; (7) yes; (8) yes; (9) yes
Study No. 9, Liswood (1995), Canada	1) IG = 18 C, CG = 18 C; (2) 10 female factor, 5 male factor, 10 both, 11 unexplained; (3) 5.9 y; (4) n. r.	(1) Randomized controlled study; (2) T: after intervention; (3) out-patient (adoption waiting list), RC; (4) 0	No IVF/ICSI, CBT, individual/couple, 6 w, 1 s for 1 h (6), total 6 h	(1) SCL-90-R; (2) SCL-90-R; (3) SCL-90-R; (4) SAS-SR; (5) participant evaluation form, evaluation from spouse; (6) no; (7) no	No sign. differences between the intervention and control group on the standardized measures. Sign. higher self and spousal improvement in the IG	(1) Both; (2) yes; (3) yes; (4) yes; (5) yes; (6) unclear; (7) yes; (8) yes; (9) yes
Study No. 10, McNaughton-Cassill *et al.* (2002), USA	(1) IG = 25 F and 16 M, CG = 19 F and 18 M; (2) n. r.; (3) IG (F): 5.7 y (3.15), CG (F): 5.81 y (2.93); (4) n. r.	(1) Controlled study; (2) T0: at begin of treatment cycle, T1: on completion of IVF treatment; (3) like IG, RC; (4) 1 F, 1 M	IVF/ICSI, couple stress management group, group/couple, 3 w, 2 s for 1.5 h, (6) total 9 h	(1) BAI; (2) BDI; (3) irrational beliefs, life orientation test; (4) no; (5) no; (6) no; (7) no	Woman reported less anxiety and men greater optimism on completion of the group sessions. Men in IG had greater numbers of irrational beliefs compared with men in CG	(1) Yes; (2) no; (3) no; (4) unclear; (5) yes; (6) unclear; (7) yes; (8) yes; (9) yes

Study No. 11, McQueeney *et al.* (1997), USA	(1) IG = 18 F, CG = 8 F; (2) 17 female factor, 2 male factor, 5 both, 5 unclear; (3) 3.8 y (SD = 15.37); (4) 4.14	(1) Controlled study; (2) T0: at first session, T1: 1 w after intervention, T2: 1 m, T3: 18 m; (3) want participate, but cannot because of scheduling problems, no; (4) 3 F	No IVF/ICSI, coping (problem- and emotion-focused), group/ woman, 6 w, 1 s for 1.5 h (6), total 9 h	(1) No; (2) BDI; (3) COPE, MHI; (4) no; (5) infertility-specific distress and well-being; (6) yes; (7) perceived control over infertility, treatment credibility, parental status	Efficacy of coping intervention in women's adjustment to infertility	(1) Yes; (2) no; (3) no; (4) yes; (5) yes; (6) >20%; (7) yes; (8) yes; (9) yes
Study No. 12, Rezabek *et al.* (2003), Czech Republic	(1) IG = 21 S, CG = 31 S; (2) n. r.; (3) n. r.; (4) n. r.	(1) Randomized controlled study; (2) T: outcome of ET; (3) like IG, no; (4) 0	IVF/ICSI, hypnosis, individual/woman, during ET	(1) No; (2) no; (3) no; (4) no; (5) no; (6) yes; (7) implantation rate, degree of relaxation	Hypnosis does not change the results of ET; subjective perception of guided relaxation was positive	(1) n.r.; (2) yes; (3) no; (4) yes; (5) yes; (6) unclear; (7) yes; (8) yes; (9) yes
Study No. 13, Sarrel and DeCherney (1985), USA	(1) IG = 10 C, CG = 9 C; (2) all secondary infertility; (3) IG: 3.7 y, CG: 3.5 y; (4) n. r.	(1) controlled study; (2) T: after 18 m; (3) like IG, RC; (4) 1 C	No IVF/ICSI, psychoanalytic counselling, individual/ couple, one interview for 2 h	(1) no; (2) no; (3) no; (4) no; (5) no; (6) yes; (7) psychological and interpersonal issues	Sign. higher pregnancy rate in IG.	(1) no; (2) no; (3) no; (4) yes; (5) yes; (6) unclear; (7) yes; (8) yes; (9) yes
Study No. 14, Schmidt *et al.* (2005), Denmark	(1) IG = 74 S, CG = 2250 S; (2) female infertility = 29% (IG,F), 36.6% (KG,F), 22.2% (IG,M), 34.8% (CG,M); male infertility = 53.3% (IG,F), 40% (CG,F), 55.6% (IG,M), 41.8% (CG,M); (3) n. r.; (4) 2 (IG, F), 2.15 (CG, F), 1.78 (IG, M), 2.18 (CG, M)	(1) Controlled study; (2) T0: before intervention, T1: 5 w, T2: 12 m; (3) cohort sample of new fertility patients, no; (4) 18 S	Mixed, communication and stress management, group/ couple, 5 w, total 18 h	(1) No; (2) no; (3) no; (4) communication with partner and with other people; (5) fertility problem stress; (6) yes; (7) fertility treatment	Intervention had a positive effect on communication, infertility related stress and seeking of information and support	(1) no; (2) no; (3) yes; (4) yes; (5) yes; (6) >40%; (7) yes; (8) unclear; (9) no
Study No. 15, Shu-Hsin (2003), China	(1) IG = 64 F, CG = 68 F; (2) IG: 17 male factor, 34 female factor, 8 both, 5 unexplained, CG: 25 male factor, 29 female factor, 7 both, 7 unexplained; (3) IG: 4.3 (2.5), CG: 4.4 (3.6); (4) IG: 2.1, CG: 2.0	(1) Randomized controlled study; (2) T0: initial stage of treatment (Day 3), T1: ET, T2: before taking the pregnancy test; (3) like IG, no; (4) 0	IVF/ICSI, nursing crisis intervention, individual/ woman, unclear	(1) STAI; (2) SDS; (3) JCS; (4) no; (5) no; (6) no; (7) infertility questionnaire	Positive effect of intervention in psychosocial responses	(1) yes; (2) yes; (3) no; (4) yes (5) yes (6) unclear (7) yes (8) yes (9) no
Study No. 16, Stewart *et al.* (1992), Canada	(1) IG = 25 M, 39 F, CG = 8 M, 27 F; (2) n. r. (3) 3 y (1.7, 0.75–9.0); (4) n. r.	(1) controlled study; (2) T0: baseline, T1: 8 w; (3) like IG, waiting list; (4) 10 S	Mixed, CB comprehensive, group/couple, woman and man, 10 w, 1 s for 2 h (8), total 16 h	(1) BSI; (2) BSI, BDI, HRDS; (3) BSI; (4) no; (5) no; (6) yes; (7) no	Sign. improvement in IG in psychological outcomes; no sign. differences in pregnancy rate between IG and CG	(1) Yes; (2) no; (3) no; (4) yes; (5) yes; (6) ≤20%; (7) yes; (8) yes; (9) no
Study No. 17, Strauss *et al.* (2002), Germany	(1) IG = 11 C and 20 F, CG = 6 F, 6 C and 12 C; (2) 69.6%: primary sterility, 32.1%: hormonal sterility, 30.2%: andrologic sterility factor, 24.5%: tubarer sterility factor, 7.5%: uterus factors, 5.7%: idiopathic sterility; (3) 52.4%: 1–3 y; (4) n. r.	(1) Randomized controlled study; (2) T0: baseline, T1: 3–4 m; (3) waiting list or patients refused counselling; (4) 6 C	No IVF/ICSI, infertility counselling, individual/ couple and woman, 9 w, total 9 h (3–15 h)	(1) No; (2) no; (3) SCL-90-R, FLZ; (4) PFB; (5) no; (6) yes; (7) assessment of value of child wish	Intensity of child wish decreased and pregnancy rate was higher after intervention	(1) Both; (2) yes; (3) no; (4) yes; (5) yes; (6) unclear; (7) yes; (8) yes; (9) no

Continued

Table I *Continued*

Reference, country	Sample	Methods	Setting and intervention	Measures	Main results	Quality indicators
Study No. 18, Tarabusi *et al.* (2004), Italy	(1) IG = 50 S, CG = 48 S; (2) n. r.; (3) 3.1 y (SD = 2.1, 1–12); (4) 18 more than one	(1) Randomized controlled study; (2) T0: baseline, T1: 4 m; (3) like IG, no; (4) 14 S	IVF/ICSI, CBT group intervention, group/couple, 4 m, 12 meetings	(1) SRT; (2) SRT; (3) SRT, Westbrook Coping Scale; (4) no; (5) no; (6) no; (7) no	CBT avoided waiting stress and stimulated discussion and awareness inside couples.	(1) Yes; (2) yes; (3) no; (4) yes; (5) yes; (6) unclear; (7) yes; (8) yes; (9) yes
Study No. 19, Tuschen-Caffier *et al.* (1999), Germany	(1) IG = 11 C, CG = 12 C; (2) all idiopathic infertility, men impairment of sperm quality; (3) IG: 42.5 m, CG: 27.4 m; (4) n. r.	(1) controlled study; (2) T0: baseline, T1: 3 m, T2: 6 m; (3) like IG, no; (4) 6 C	No IVF/ICSI, sex therapy, individual/couple, 24 w	(1) No; (2) no; (3) no; (4) self-rating; (5) self-rating; (6) yes; (7) KINT	Therapy group showed improvement in sperm concentration and sexual behaviour, reduction in thoughts of helplessness and decrease in marital distress	(1) Both; (2) no; (3) no; (4) yes; (5) yes; (6) unclear; (7) no; (8) no; (9) yes
Study No. 20, Wischmann *et al.* (2001a, b, 2002), Germany	(1) IG = 110 C and 24 C, CG = 23 C; (2) unexplained: 48% CG, 34% counselling, 58% therapy; (3) CG: 4.7 y (2.6), counselling: 4.5 y (2.9), therapy: 4.7 y (2.9); (4) n. r.	(1) Randomized controlled study; (2) T0: baseline, T1: 3 m; (3) like IG, waiting list; (4) n. r.	Mixed, counselling and couple-therapy, individual/couple, 2 or 10 w, 2 s for 2 h or 10 s for 1 h, total 2 h or 10 h	(1) SCL-90-R; (2) SCL-90-R; (3) SCL-90-R; (4) no; (5) no; (6) yes; (7) FKW	Couple-therapy showed stronger effects than counselling compared with control group.	(1) Yes; (2) yes; (3) no; (4) yes; (5) yes; (6) unclear; (7) unclear; (8) unclear; (9) no
Study No. 21, Zhen *et al.* (2005), China	(1) IG = 258 F, CG = 258 F; (2) secondary infertility; (3) ≥3 y; (4) n. r.	(1) Randomized controlled study; (2) T0: baseline, T1: 6 w, T2: 3 m; (3) like IG, simulative restriction treatment; (4) 0	No IVF/ICSI, psychological supportive therapy, behavioural therapy, rational emotive therapy, individual/couple, 6 w, 1 s for 20–40 min (3–12), total 2–4 h	(1) Anxiety scale; (2) depression scale; (3) no; (4) no; (5) no; (6) no; (7) symptoms of insomnia	Psychological intervention helped more for infertile person than control treatment	(1) No; (2) yes; (3) no; (4) yes; (5) no; (6) unclear; (7) yes; (8) yes; (9) yes

Time of measurement: t, time; T0, baseline; T1, post; T2, follow-up; IG, intervention group; CG, control group. Medical: PCOS, polycystic ovary syndrome; ET, embryo transfer; IVF, *in vitro* fertilization; ICSI, intra cytoplasmic sperm injection. Intervention: CBT, cognitive behavioural therapy; CB, cognitive behavioural. Measures: AN, Anamnesefragebogen; AnEx, Spielberger Anger Expression Scale; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; COPE, coping strategies; DEBQ, Dutch Eating Behaviour Questionnaire; DRK, Daily Record Keeping Chart; DSFI, Derogatis Sexual Functioning Inventory; EPI, Eysenck Personality Inventory; EPQ, Eysenck Personality Questionnaire; FAI, feelings about infertility; FIQ, Fertility Information Questionnaire; FKW, Fragebogen zur Kinderwunschstärke; FLZ, Fragebogen zur Lebenszufriedenheit; FPI, Fertility Problem Inventory; GHH, General Hospital Anxiety and Depression Scale; GHQ, General Health Questionnaire; HADS, Hospital Anxiety and Depression Scale; HRDS, Hamilton Depression Rating Scale; IPC-PL, Fragebogen zur Kontrollüberzeugung in Problemsituationen; ISE, Infertility Self-Efficacy Scale; JCS, Jalowiec Coping Scale; KINT, Kognitionen in Infertilität; MAS, Marital Adjustment Scale; MDS, Marital Distress Scale; MHI, Mental Health Inventory; MHV, Mill Hill Vocabulary Scale; PFB, Partnerschaftsfragebogen; PNSS, Perceived Negative Support Scale; POMS, Profile Of Mood States; RDAS, Revised Dyadic Adjustment Scale; RSES, The Rosenberg Self-Esteem Scale; SAS, Self-Assessment Scale; SAS-SR, Social Adjustment Scale—Self-Report; SB, Situationsbewertungssystem; SCL-90-R, Symptom Checklist-90-R; SDS, Zung Self-reported Depression Scale; SES, Self-Esteem Scale; SEX, Fragebogen zur Sexualität; SI, IVF Stress Inventory; SN, Schriftliche Nachbefragung; SRT, symptom rating test; STAI, State-Trait Anxiety Inventory; TMAS, Taylor Manifest Anxiety Scale; VEV, Veränderungsfragebogen des Erlebens und Verhaltens; WIQ, Waring Intimacy Questionnaire; WOC, Ways of Coping Scale; 16PF, 16 Personality Factor Questionnaire. Quality indicators: (1) Standardized measures of psychological outcomes; (2) Randomization; (3) Blinding; (4) IG comparable to CG; (5) Comparable care; (6) Dropouts before allocation; (7) Dropouts during study ≤20%; (8) ≤20% difference of dropouts in IG and CG; (9) Inclusion criteria reported. Others: F, female; M, male; C, couple; S, subject; y, year(s); m, month(s); w, week(s); h, hour(s); min, minute(s); s, session(s); n. r., not reported; M, mean; RC, routine care; sign., significant; SD, standard deviation.

receive any specific intervention. In 10 of the studies, the control group received routine care or information.

The study quality of all 21 studies was comprehensively assessed according to nine criteria (Table I). There were 10 studies that reported standardized measures of psychological outcomes (depression, anxiety, mental distress, infertility-specific stress and interpersonal functioning); 3 studies used non-standardized measures and 4 studies employed both the measures. In four of the studies, it was not clearly stated whether standardized or non-standardized measures were used. Only three studies used a blinded assessment of outcomes and group membership. In 19 of the studies, the intervention group sample and the control group sample were rated as comparable (the sociodemographic and clinical characteristics of the control and the intervention group samples were not comparable in Facchinetti *et al*., 2004; McNaughton-Cassill *et al*., 2002). Most of the studies, with the exception of Zhen *et al*. (2005), provided comparable care in both the intervention and the control groups. There were five studies that had 20% or fewer participant dropouts before allocation to intervention or control group. McQueeney *et al*. (1997) reported >20% participant dropouts, while three studies (De Klerk *et al*., 2005; Schmidt *et al*., 2005; Chan *et al*., 2006) had >40% participant dropouts (14 studies did not provide clear information on this item). Twenty per cent or fewer participant dropouts were reported in 13 studies during the course of study. A total of 15 studies reported 20% or less difference in their participant dropout rate between intervention and control groups. Clear inclusion criteria were described in 16 studies, whereas 5 studies did not report on such criteria at all.

Efficacy of psychological interventions

Psychological measures

There were 12 studies that reported on the efficacy of psychological interventions with respect to depressive symptoms (Figure 1). The overall ES was 0.17 (99% CI: −0.24, 0.58), indicating a non-significant effect for psychological interventions with respect to depressive symptoms. There was a high amount of heterogeneity between studies ($Chi^2 = 94.35$; d.f. = 11; $P \leq 0.00001$; $I^2 = 88\%$). This heterogeneity could primarily be attributed to one large study (Zhen *et al*., 2005) that had a large ES for depression ($d = 0.97$). After excluding this study, the non-significant overall ES of psychological interventions dropped to 0.02, with regard to depression. This ES was based on moderate homogeneous results. Exclusion of the Zhen study led to a considerable decrease in heterogeneity between the studies, producing I^2 values <50%, which suggests a more reliable point estimate for the effect of the psychological treatments.

Anxiety was assessed in 12 studies (Figure 2), which pooled together produced an overall non-significant ES of 0.16 (99% CI: −0.10, 0.42) for all types of anxiety measures. This pooled effect was based on highly heterogeneous ES between the original studies ($Chi^2 = 80.32$; d.f. = 15; $P \leq 0.00001$; $I^2 = 81\%$). Again, the high heterogeneity could be attributed to Zhen *et al*. (2005). After excluding this study, the overall non-significant ES was 0.06 (99% CI: −0.10, −0.23) for all types of anxiety measures, based on marginally heterogeneous primary studies ($Chi^2 = 23.95$; d.f. = 14; $P = 0.05$; $I^2 = 42\%$). State anxiety decreased with a non-significant effect of 0.12. There was no overall effect for psychological interventions with respect to trait anxiety: the ES was −0.08 (99% CI: −0.37, 0.20). These pooled ES for state and trait anxiety were based on moderate homogeneous results between individual studies: state anxiety (Figure 3) and trait anxiety ($Chi^2 = 4.80$; d.f. = 3; $P = 0.19$; $I^2 = 38\%$).

The results of the meta-analyses for mental distress, interpersonal functioning and infertility-specific stress are described below (without figure). Mental distress was assessed in eight studies, resulting in an overall non-significant ES of 0.08 (99% CI: −0.10, 0.51). There were five studies that reported on interpersonal functioning, resulting in an overall non-significant ES of 0.01 (99% CI: −0.26, 0.29). The effect of psychological interventions on infertility-specific stress was assessed in five studies; infertility-specific stress was not significantly reduced by psychological interventions registering an ES of 0.10 (99% CI: −0.35, 0.54). The overall ES for mental distress and

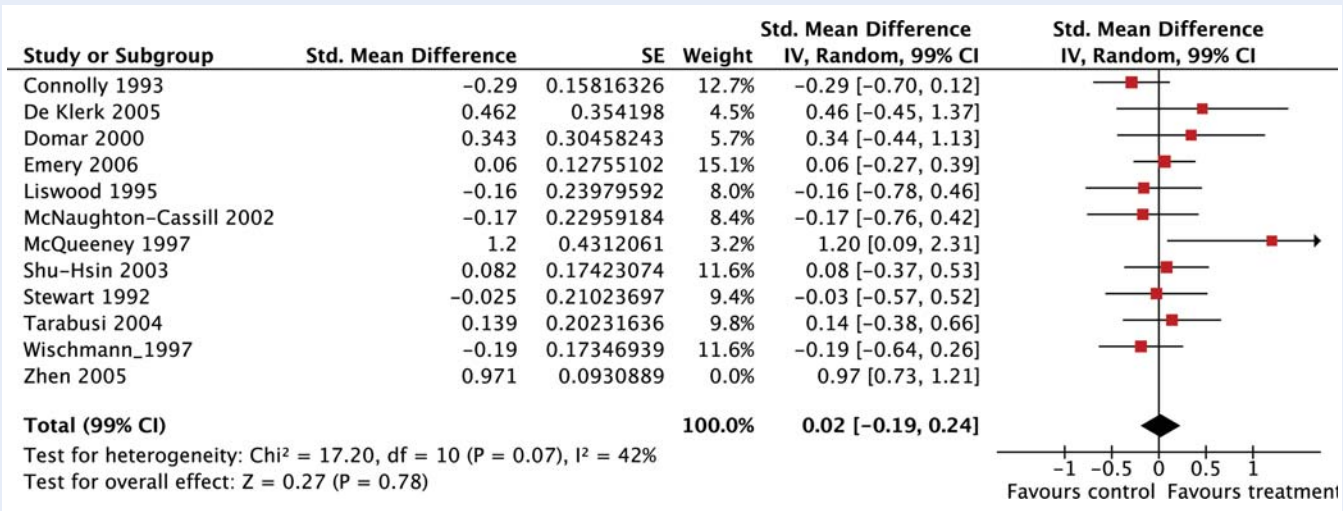

Figure 1 Effect of psychological interventions on depression (after excluding Zhen *et al*., 2005).

Abbreviations: 99%CI, 99% confidence interval; df, degree of freedom; *P*, probability value; *Z*, standard score; Chi^2, chi-square value; SE, standard error; Std. Mean Difference, standard mean difference; IV, inverse variance.

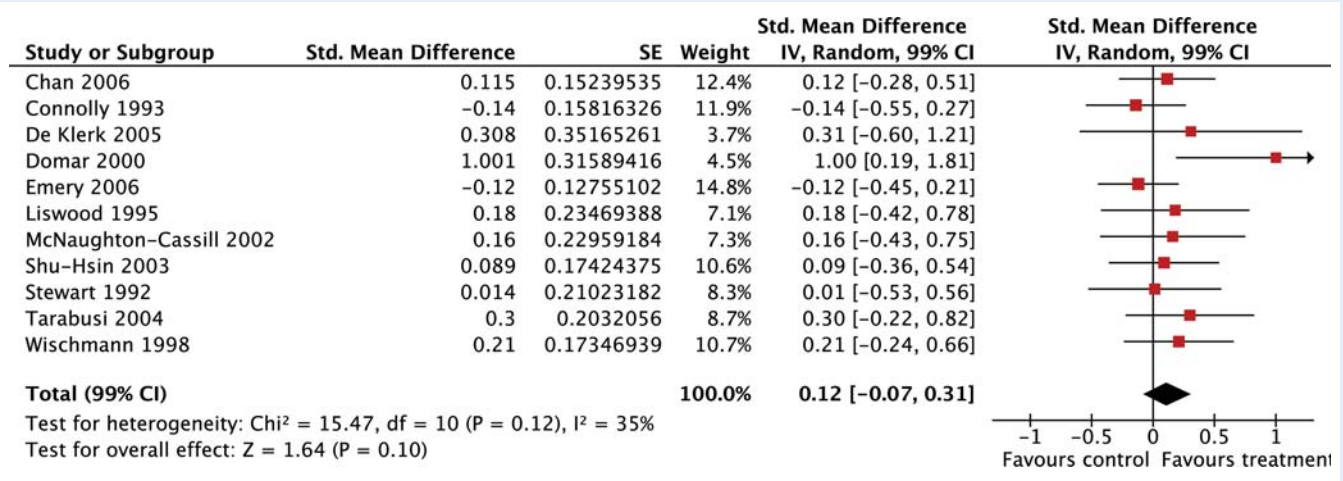

Figure 2 Effect of psychological interventions on state anxiety.

Abbreviations: 99%CI, 99% confidence interval; df, degree of freedom; *P*, probability value; *Z*, standard score; Chi^2, chi-square value; SE, standard error; Std. Mean Difference, standard mean difference; IV, inverse variance.

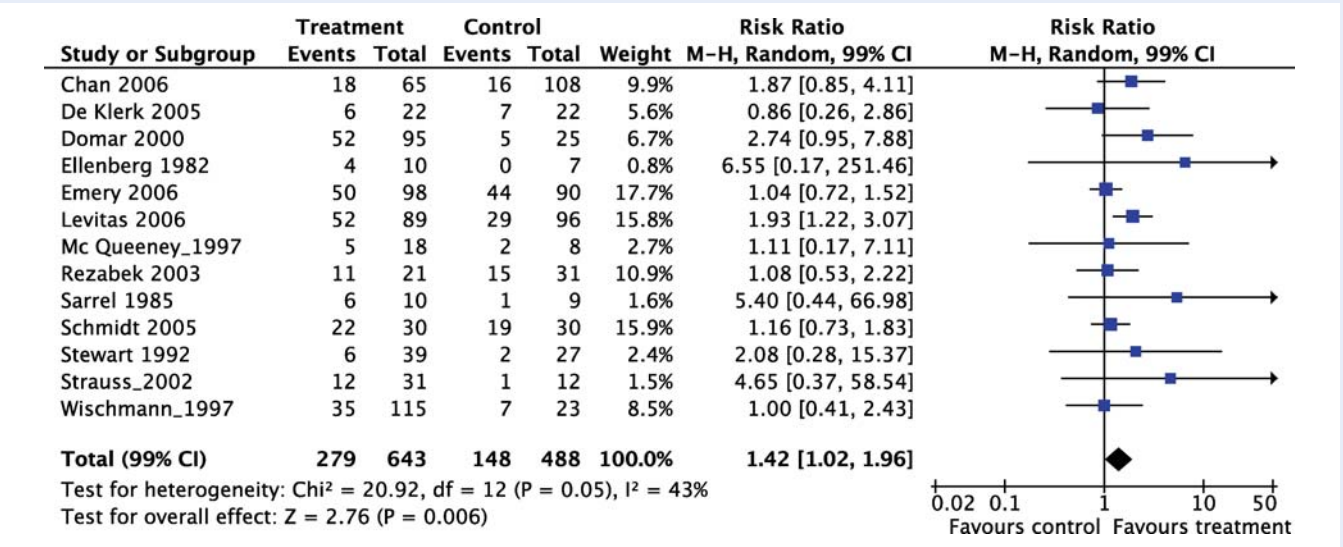

Figure 3 Effect of psychological interventions on pregnancy rate.

Abbreviations: 99%CI, 99% confidence interval; df, degree of freedom; *P*, probability value; *Z*, standard score; Chi^2, chi-square value; SE, standard error; Std. Mean Difference, standard mean difference; M–H, Mantel–Haenszel.

interpersonal functioning was based on homogeneous results between studies, whereas the ES for infertility-specific stress was based on heterogeneous results between studies: (mental distress: $Chi^2 = 12.34$; d.f. = 7; $P = 0.09$; $I^2 = 43\%$; interpersonal functioning: $Chi^2 = 3.34$; d.f. = 4; $P = 0.50$; $I^2 = 0\%$; infertility-specific stress: $Chi^2 = 10.67$; d.f. = 4; $P = 0.03$; $I^2 = 62\%$).

Pregnancy rate

The psychological interventions were shown to have a significant effect on pregnancy rate with a risk ratio (RR) of 1.42 based on homogeneous primary studies. The RR of 1.42 (99% CI: 1.02, 1.96) can be seen as equivalent to a number needed to treat of 5 assuming a pregnancy rate of 30% in the control group, or a number needed to treat of 7 if half of the patients will be pregnant in the control group. When 13 trials that provided data for an ITT analysis (assuming patients lost to FU did not achieve pregnancy) were analysed, the pooled pregnancy rate estimate was slightly higher (RR 1.48, 99% CI: 0.98, 2.21). There was moderate heterogeneity between the individual studies ($Chi^2 = 28.62$; d.f. = 12; $P = 0.004$; $I^2 = 58\%$; analysis not shown in a figure). This RR of the ITT analysis can be seen as equivalent to a number needed to treat of 4 if 30% of the control group patients achieve pregnancy and a number needed to treat of 6 if 50% were assumed to become pregnant.

Subgroup analysis

A subgroup analysis for sex, duration of intervention, ART and randomization was performed to analyse variables moderating the effect of psychological interventions between the studies (Table II). No significant effects on psychological outcomes were found in separate analyses among women and men following psychological interventions. Further, no significant ES difference for psychological measures was found between women and men.

A second subgroup analysis was performed that looked at intervention duration (Table II). Longer psychological interventions (six or more sessions) demonstrated ES statistically comparable with those of shorter interventions (five or fewer sessions) for all psychological outcomes (e.g. state anxiety: $d = 0.28$ versus $d = 0.07$; mental distress: $d = 0.26$ versus $d = 0.09$). Out of six psychological outcome measures assessed, only one ES difference was found which was significant—that of anxiety ($P = 0.007$)—and pointed to a benefit of longer interventions. With respect to pregnancy rate, longer psychological interventions (FU data only: RR 1.87; $P = 0.07$) were not significantly more effective than shorter interventions (FU data only: RR 1.33; $P = 0.05$). Regarding pregnancy rate, the overall ES of long interventions was based on homogeneous original studies, whereas the estimates for short psychological interventions were based on the nearly homogeneous ES of the original studies.

A third subgroup analysis was performed looking at medical treatment type. The studies were grouped according to the criteria of whether the women underwent assisted reproductive treatment or not (ART: IVF/ICSI versus no IVF/ICSI; Table II). Regarding psychological outcomes, no significant overall ES was found for psychological interventions in those studies where patients did not receive IVF/ICSI treatment. However, with respect to pregnancy rate, psychological interventions were significantly effective (FU data only: RR 2.73; ITT: RR 4.06) only in cases where patients were not treated with IVF/ICSI than those treated with IVF/ICSI (FU data only: RR 1.34; ITT: RR 1.29). Both estimates of non-IVF/ICSI treated patients were based on the highly homogeneous ES of the original studies. There was a large difference between IVF/ICSI and no IVF/ICSI in the RR of the pregnancy rate at FU (RR 1.39) and the RR of the pregnancy rate resulting from the ITT analysis (RR 2.77). However, the ES differences were not statistically significant different for pregnancy rate in FU studies ($P = 0.19$) and for ITT analysis ($P = 0.09$).

A further subgroup analysis was conducted on those studies that used randomization for their allocation of patients (Table II). Conducting a conservative estimate using randomized controlled studies revealed no significant overall ES with respect to any psychological outcomes. Non-randomized studies also failed to display any significant overall ES. Non-randomized studies indicated slightly higher overall effects of psychological interventions with regard to one's chances of becoming pregnant (FU data only: RR 1.63; ITT: RR 1.65) versus randomized studies (FU data only: RR 1.31; ITT: RR 1.38). With the exception of infertility-specific distress ($P = 0.002$), no significant ES differences were found with respect to any psychological outcomes. The ES differences were not significant for pregnancy FU ($P = 0.36$) and for ITT analysis ($P = 0.40$).

Exploration of publication bias

Use of a funnel plot revealed markedly symmetrical results with respect to interpersonal functioning and infertility-specific stress. Unsymmetrical results were found with respect to depression, anxiety, state anxiety, trait anxiety, mental distress and pregnancy. The latter results can be interpreted as a hint of possible publication bias, as smaller studies that did not demonstrate efficacy might not have been published.

Discussion

The results of this meta-analysis of psychological interventions for patients suffering from infertility do not indicate their overall efficacy with respect to mental health. However, some evidence was found for the efficacy of psychological interventions in achieving pregnancy. With respect to mental health, the findings of this meta-analysis on efficacy stand in contrast to the results of Boivin (2003) and de Liz and Strauss (2005); however, its findings pointing to an increased pregnancy rate due to psychological interventions are in line with the two previous reviews. The differences in results concerning mental health may be attributed to the present meta-analysis' strict criteria for inclusion (controlled studies only) versus those of other reviews, which encompass mixed study designs, including pre–post comparison studies.

As the present results indicate no significant effects in general for psychological interventions in connection with mental health, they run somewhat counter to research results in other areas of behavioural medicine where efficacy has been shown. However, it is important to note that in behavioural medicine psychological interventions for distressed patients have proven less effective than interventions for patients with mental disorders only. Psychological interventions have only demonstrated small effects among patients with somatic illnesses: type 1 diabetes patients have improved through psychological intervention registering an ES of 0.26 (Winkley *et al*., 2006); patients with lower back pain have displayed non-significantly reduced depressive symptoms registering an ES of 0.34 (Hoffman *et al*., 2007); depressed coronary heart disease patients have improved through psychological or psychopharmacological intervention registering ES ranging from 0.30 to 0.35 (Lespérance *et al*., 2007). Further, it is important to note that, contrary to some of the types of patient groups described above, patients with infertility generally exhibit good mental health (Dunkel-Schetter and Lobel, 1991; Eugster and Vingerhoets, 1999; Wischmann, 2005). There is also general agreement among researchers that high levels of depressive symptoms, anxiety and distress among infertile patients are possibly only short-term reactions to infertility and its treatment medically. This could lead to a floor effect for psychological interventions. The small ES of psychological interventions for infertile patients might also be explained by emotional adjustment processes, which are present in patients not receiving psychological interventions as well.

As mentioned, the present results also indicate that psychological interventions may be effective in increasing couples' pregnancy rate. However, this result only provides answers regarding the average effect of psychological interventions on pregnancy rate. The positive effect on pregnancy must be interpreted cautiously since higher effects were found in non-randomized studies (trend) and a clear

Table II Subgroup analyses for sex, duration of intervention, ART and randomization: ES and RR

	Depression	Anxiety	State anxiety	Mental distress	Interpersonal functioning	Infertility-specific stress	Pregnancy follow-up (FU)	Pregnancy ITT
Sex								
Male	$d = -0.09$, 99%CI: −0.34 to 0.16, $N = 7$, $P = 0.35$	$d = 0.04$, 99%CI: −0.16 to 0.24, $N = 7$, $P = 0.59$	$d = 0.07$, 99%CI: −0.15 to 0.29, $N = 8$, $P = 0.41$	$d = 0.06$, 99%CI: −0.26 to 0.38, $N = 6$, $P = 0.62$	$d = 0.06$, 99%CI: −0.45 to 0.58, $N = 3$, $P = 0.75$	$d = -0.05$, 99%CI: −0.48 to 0.38, $N = 4$, $P = 0.77$	Not applicable	Not applicable
	$Chi^2 = 6.39$, d.f. = 6, $P = 0.38$, $I^2 = 6\%$	$Chi^2 = 4.03$, d.f. = 8, $P = 0.85$, $I^2 = 0\%$	$Chi^2 = 3.39$, d.f. = 7, $P = 0.85$, $I^2 = 0\%$	$Chi^2 = 6.25$, d.f. = 5, $P = 0.28$, $I^2 = 20\%$	$Chi^2 = 0.03$, d.f. = 2, $P = 0.99$, $I^2 = 0\%$	$Chi^2 = 5.17$, d.f. = 3, $P = 0.16$, $I^2 = 42\%$		
Female	$d = 0.06$, 99%CI: −0.22 to 0.35, $N = 10$, $P = 0.56$	$d = 0.06$, 99%CI: −0.13 to 0.24, $N = 15$, $P = 0.42$	$d = 0.15$, 99%CI: −0.09 to 0.38, $N = 11$, $P = 0.18$	$d = 0.26$, 99%CI: −0.04 to 0.56, $N = 8$, $P = 0.02$	$d = 0.01$, 99%CI: −0.29 to 0.31, $N = 5$, $P = 0.95$	$d = 0.19$, 99%CI: −0.35 to 0.72, $N = 5$, $P = 0.37$		
	$Chi^2 = 16.81$, d.f. = 9, $P = 0.06$, $I^2 = 45\%$	$Chi^2 = 23.22$, d.f. = 14, $P = 0.06$, $I^2 = 40\%$	$Chi^2 = 15.09$, d.f. = 10, $P = 0.13$, $I^2 = 34\%$	$Chi^2 = 9.33$, d.f. = 7, $P = 0.23$, $I^2 = 25\%$	$Chi^2 = 3.36$, d.f. = 4, $P = 0.50$, $I^2 = 0\%$	$Chi^2 = 10.86$, d.f. = 4, $P = 0.03$, $I^2 = 63\%$		
Comparison test z-value (P-value)	−1.01 ($P = 0.16$)	−0.19 ($P = 0.42$)	−0.65 ($P = 0.26$)	−1.18 ($P = 0.12$)	0.21 ($P = 0.58$)	−0.91 ($P = 0.18$)		
Duration of intervention								
Short intervention (≤5 sessions)	$d = -0.07$, 99%CI: −0.39 to 0.25, $N = 4$, $P = 0.59$	$d = -0.04$, 99%CI: −0.22 to 0.13, $N = 7$, $P = 0.50$	$d = 0.07$, 99%CI: −0.16 to 0.30, $N = 5$, $P = 0.88$	$d = 0.09$, 99%CI: −0.56 to 0.74, $N = 2$, $P = 0.73$	$d = -0.16$, 99%CI: −0.61 to 0.29, $N = 1$, $P = 0.37$	$d = 0.09$, 99%CI: −0.41 to 0.59, $N = 3$, $P = 0.65$	RR = 1.33, 99%CI: 0.89–2.00, $N = 7$, $P = 0.07$	RR = 1.27, 99%CI: 0.85–1.88, $N = 7$, $P = 0.13$
	$Chi^2 = 5.71$, d.f. = 3, $P = 0.13$, $I^2 = 47\%$	$Chi^2 = 7.37$, d.f. = 6, $P = 0.29$, $I^2 = 19\%$	$Chi^2 = 4.46$, d.f. = 4, $P = 0.35$, $I^2 = 10\%$	$Chi^2 = 1.84$, d.f. = 1, $P = 0.18$, $I^2 = 46\%$	Not applicable	$Chi^2 = 5.67$, d.f. = 2, $P = 0.06$, $I^2 = 65\%$	$Chi^2 = 12.70$, d.f. = 6, $P = 0.05$, $I^2 = 53\%$	$Chi^2 = 11.89$, d.f. = 6, $P = 0.06$, $I^2 = 50\%$
Long intervention (6 and more session)	$d = 0.11$, 99%CI: −0.26 to 0.49, $N = 6$, $P = 0.43$	$d = 0.30$, 99%CI: −0.02 to 0.61, $N = 6$, $P = 0.02$	$d = 0.28$, 99%CI: −0.08 to 0.64, $N = 5$, $P = 0.05$	$d = 0.26$, 99%CI: −0.11 to 0.64, $N = 6$, $P = 0.07$	$d = 0.12$, 99%CI: −0.23 to 0.47, $N = 4$, $P = 0.39$	$d = 0.19$, 99%CI: −1.22 to 1.61, $N = 2$, $P = 0.72$	RR = 1.87, 99%CI: 0.81–4.32, $N = 6$, $P = 0.05$	RR = 2.41, 99%CI: 0.73–7.91, $N = 6$, $P = 0.06$
	$Chi^2 = 10.00$, d.f. = 5, $P = 0.08$, $I^2 = 50\%$	$Chi^2 = 7.6$, d.f. = 5, $P = 0.18$, $I^2 = 34\%$	$Chi^2 = 7.21$, d.f. = 4, $P = 0.13$, $I^2 = 45\%$	$Chi^2 = 9.34$, d.f. = 5, $P = 0.10$, $I^2 = 46\%$	$Chi^2 = 1.81$, d.f. = 3, $P = 0.61$, $I^2 = 0\%$	$Chi^2 = 4.96$, d.f. = 1, $P = 0.03$, $I^2 = 80\%$	$Chi^2 = 9.76$, d.f. = 5, $P = 0.08$, $I^2 = 49\%$	$Chi^2 = 17.39$, d.f. = 5, $P = 0.004$, $I^2 = 71\%$
Comparison test z-value (P-value)	−0.93 ($P = 0.18$)	−2.45 ($P = 0.007$)	−1.27 ($P = 0.10$)	−0.58 ($P = 0.28$)	−1.27 ($P = 0.10$)	−0.17 ($P = 0.43$)	−0.41 ($P = 0.34$)	−0.57 ($P = 0.28$)
ART								
IVF/ICSI	$d = 0$, 99%CI: −0.23 to 0.22, $N = 6$, $P = 0.96$	$d = -0.03$, 99%CI: −0.17 to 0.11, $N = 10$, $P = 0.57$	$d = 0.03$, 99%CI: −0.14 to 0.20, $N = 7$, $P = 0.61$	$d = 0.15$, 99%CI: −0.30 to 0.61, $N = 2$, $P = 0.38$	$d = -0.16$, 99%CI: −0.61 to 0.29, $N = 1$, $P = 0.37$	$d = 0.12$, 99%CI: −0.47 to 0.23, $N = 2$, $P = 0.37$	RR = 1.34, 99%CI: 0.86–2.08, $N = 5$, $P = 0.09$	RR = 1.29, 99%CI: 0.86–1.93, $N = 5$, $P = 0.10$
	$Chi^2 = 6.52$, d.f. = 5, $P = 0.26$, $I^2 = 23\%$	$Chi^2 = 9.63$, d.f. = 9, $P = 0.38$, $I^2 = 7\%$	$Chi^2 = 5.67$, d.f. = 6, $P = 0.46$, $I^2 = 0\%$	$Chi^2 = 0.89$, d.f. = 1, $P = 0.35$, $I^2 = 0\%$	Not applicable	$Chi^2 = 0.69$, d.f. = 1, $P = 0.41$, $I^2 = 0\%$	$Chi^2 = 9.91$, d.f. = 4, $P = 0.04$, $I^2 = 60\%$	$Chi^2 = 8.01$, d.f. = 4, $P = 0.09$, $I^2 = 50\%$
No IVF/ICSI	$d = 0.39$, 99%CI: −0.54 to 1.32, $N = 3$, $P = 0.28$	$d = 0.51$, 99%CI: −0.11 to 1.13, $N = 2$, $P = 0.03$	$d = 0.56$, 99%CI: −0.49 to 1.62, $N = 2$, $P = 0.17$	$d = 0.40$, 99%CI: −0.25 to 1.05, $N = 4$, $P = 0.12$	$d = 0.12$, 99%CI: −0.23 to 0.47, $N = 4$, $P = 0.39$	$d = 0.19$, 99%CI: −1.22 to 1.61, $N = 2$, $P = 0.72$	RR = 2.73, 99%CI: 1.23–6.05, $N = 5$, $P = 0.001$	RR = 4.06, 99%CI: 1.72–9.59, $N = 5$, $P < 0.0001$
	$Chi^2 = 7.84$, d.f. = 2, $P = 0.02$, $I^2 = 74\%$	$Chi^2 = 4.35$, d.f. = 2, $P = 0.11$, $I^2 = 54\%$	$Chi^2 = 4.35$, d.f. = 1, $P = 0.04$, $I^2 = 77\%$	$Chi^2 = 8.43$, d.f. = 3, $P = 0.04$, $I^2 = 64\%$	$Chi^2 = 1.81$, d.f. = 3, $P = 0.61$, $I^2 = 0\%$	$Chi^2 = 4.96$, d.f. = 1, $P = 0.03$, $I^2 = 80\%$	$Chi^2 = 2.79$, d.f. = 4, $P = 0.59$, $I^2 = 0\%$	$Chi^2 = 4.11$, d.f. = 4, $P = 0.39$, $I^2 = 3\%$

Comparison test z-value (*P*-value)	−1.05 ($P = 0.15$)	−2.19 ($P = 0.02$)	−1.27 ($P = 0.102$)	−0.81 ($P = 0.21$)	−1.27 ($P = 0.102$)	−0.13 ($P = 0.45$)	−0.88 ($P = 0.19$)	−1.35 ($P = 0.09$)
Randomization								
Yes	$d = -0.01$, 99%CI: −0.21 to 0.19, $N = 8$, $P = 0.90$	$d = 0.07$, 99%CI: −0.12 to 0.25, $N = 13$, $P = 0.35$	$d = 0.14$, 99%CI: −0.09 to 0.36, $N = 9$, $P = 0.12$	$d = 0.13$, 99%CI: −0.19 to 0.44, $N = 6$, $P = 0.29$	$d = 0.03$, 99%CI: −0.30 to 0.35, $N = 4$, $P = 0.83$	$d = -0.16$, 99%CI: −0.47 to 0.15, $N = 3$, $P = 0.65$	RR = 1.31, 99%CI: 0.85–2.01, $N = 7$, $P = 0.11$	RR = 1.38, 99%CI: 0.77–2.49, $N = 7$, $P = 0.16$
	$Chi^2 = 8.84$, d.f. = 7, $P = 0.26$, $I^2 = 21\%$	$Chi^2 = 23.61$, d.f. = 12, $P = 0.02$, $I^2 = 49\%$	$Chi^2 = 15.25$, d.f. = 8, $P = 0.05$, $I^2 = 48\%$	$Chi^2 = 7.50$, d.f. = 5, $P = 0.19$, $I^2 = 33\%$	$Chi^2 = 3.33$, d.f. = 3, $P = 0.34$, $I^2 = 10\%$	$Chi^2 = 5.67$, d.f. = 2, $P = 0.06$, $I^2 = 65\%$	$Chi^2 = 10.68$, d.f. = 6, $P = 0.10$, $I^2 = 44\%$	$Chi^2 = 18.60$, d.f. = 6, $P = 0.005$, $I^2 = 68\%$
No	$d = 0.23$, 99%CI: −0.59 to 1.05, $N = 3$, $P = 0.48$	$d = 0.08$, 99%CI: −0.32 to 0.48, $N = 2$, $P = 0.60$	$d = 0.08$, 99%CI: −0.32 to 0.48, $N = 2$, $P = 0.60$	$d = 0.55$, 99%CI: −0.51 to 1.60, $N = 2$, $P = 0.18$	$d = -0.01$, 99%CI: −0.72 to 0.70, $N = 1$, $P = 0.97$	$d = 0.43$, 99%CI: −0.02 to 0.84, $N = 2$, $P = 0.72$	RR = 1.63, 99%CI: 0.94–2.84, $N = 6$, $P = 0.02$	RR = 1.65, 99%CI: 0.96–2.84, $N = 6$, $P = 0.02$
	$Chi^2 = 8.16$, d.f. = 2, $P = 0.02$, $I^2 = 75\%$	$Chi^2 = 0.22$, d.f. = 1, $P = 0.64$, $I^2 = 0\%$	$Chi^2 = 0.22$, d.f. = 1, $P = 0.64$, $I^2 = 0\%$	$Chi^2 = 3.09$, d.f. = 1, $P = 0.08$, $I^2 = 68\%$	not applicable	$Chi^2 = 4.96$, d.f. = 1, $P = 0.03$, $I^2 = 80\%$	$Chi^2 = 8.29$, d.f. = 5, $P = 0.14$, $I^2 = 40\%$	$Chi^2 = 7.45$, d.f. = 5, $P = 0.19$, $I^2 = 33\%$
Comparison test z-value (*P*-value)	−0.73 ($P = 0.23$)	−0.06 ($P = 0.52$)	0.34 ($P = 0.63$)	−0.99 ($P = 0.16$)	0.13 ($P = 0.55$)	−2.96 ($P = 0.002$)	−0.35 ($P = 0.36$)	−0.25 ($P = 0.401$)

d, effect size; CI, confidence interval; RR, risk ratio; *N*, number of results; Chi^2, Chi-square value; I^2, test for heterogeneity; d.f., degree of freedom for test of heterogeneity; ITT, intention to treat.
Formula: *z*-value of ES difference $= ES_1 - ES_2/\sqrt{SE_1^2 + SE_2^2}$; *z*-value of $RR_{Difference} = RR_1 - RR_2/\sqrt{SE_1^2 + SE_2^2}$.

explanation for this effect cannot be provided. One explanation for couples' increased rate of pregnancy following psychological interventions could be as follows: sexual activity is disrupted—at least temporarily—in more than half of the couples suffering from infertility (Wischmann, 2003). Psychological interventions may positively impact sexual behaviour, particularly among couples not receiving ART, and thus increase their chances of becoming pregnant on this basis alone. Although sexual behaviour was not evaluated in the present review, Boivin (2003) has found that all the relevant psychological intervention studies that assessed couples' sexual behaviour registered a positive effect with respect to their frequency of sexual intercourse. Such increased rates of sexual intercourse following psychological interventions may provide a link to the increased rates of pregnancy. In order to arrive at a definitive conclusion, infertile patients' sexual behaviour and their mental distress would have to be assessed simultaneously to determine their relative effect on the pregnancy rate. Thus, future studies should be sure to evaluate couples' frequency of sexual activity and their sexual satisfaction. A further explanation for increases in pregnancy rate among infertile patients following psychological interventions may be the dropout rates in ART. The overall success of ART in terms of cumulative pregnancy rates is strongly influenced by early cessation of treatment. High levels of anxiety and depression in infertile patients and the use of a standard treatment strategy for IVF and ICSI are associated with a higher dropout rate (Smeenk *et al*., 2004; Verberg *et al*., 2008).

A subgroup analysis examining the gender effect of psychological interventions indicated that psychological interventions might be more beneficial for women (trend). In general, women registered greater ES across all psychological outcomes in response to psychological interventions. However, of these, no effect and no ES difference could be considered significant. In contrast, no treatment effects—even negative treatment effects—were found among men. There is, therefore, some preliminary evidence that women suffering from infertility benefit more from psychological interventions than their male counterparts. These results could be explained by differences between the sexes in their psychological responses to infertility: several studies have shown that women experience higher levels of mental distress than men (Wright *et al*., 1991; Wischmann, 2005; Covington and Burns, 2006). Seeking to explain women's higher levels of mental distress in this regard, two hypothesis have been discussed (Dunkel-Schetter and Stanton, 1991): (i) women must bear the primary burden of medical treatment for infertility and (ii) their wish for a child is more important to their life's plan and in comparison with men, they have fewer available alternatives with which to stabilize their self-esteem (Abbey *et al*., 1992; Edelmann *et al*., 1994). The present study does not provide additional information on these assumptions. However, from a clinical perspective, women are more often willing to look for and participate in psychological interventions (Stanton *et al*., 1991; Beaurepaire *et al*., 1994). Since the results of the present study point to some beneficial effects of psychological interventions among women in particular, offering women psychological support might be considered an efficient option in response to the greater burden they experience in association with infertility. This result can be seen as an important contribution to further research.

The present meta-analysis also found that, with respect to pregnancy rate, psychological interventions are effective (in trend) in particular for patients not receiving ART. This result may be

confounded by the duration of infertility and the duration of the interventions. The mean duration of infertility among patients receiving ART was ~4.8 years; among patients not receiving ART, the mean duration of infertility was ~3.5 years. ART are conducted after a comprehensive diagnostic exploration, once it has been decided that a patient's fertility disorder will not respond to other medical treatments. In addition, the present analysis revealed that patients receiving ART participated in psychological interventions that were markedly shorter in duration, averaging 3.6 sessions (1–12 sessions), when compared with the psychological interventions visited by patients not receiving ART, which averaged 9.8 sessions (2–20 sessions). Boivin (2003) reported that psychological interventions of a longer duration—between 6 and 12 weeks—are more effective. The results of the present study appear to point in the same direction. In a subgroup analysis examining the duration of the interventions, higher ES were found for longer interventions (six or more sessions); however, only one of the ES differences between longer and shorter interventions could be labelled significant. Short interventions did not display any effects even negative effects on infertile patients' mental health. From the perspective of clinicians, it does not appear promising to offer psychological treatments of five or fewer sessions.

Owing to the dearth of relevant studies available, a subgroup analysis focussing on the types of psychological interventions was not conducted in the present meta-analysis. The studies included in the present meta-analysis can be organized into six groups according to the intervention strategies (see description) they employed. As there were no more than six studies for any one treatment strategy and because the studies did not all assess the same outcome measures, the present meta-analysis could not provide any information concerning the individual efficacy of different types of interventions for infertile patients.

There are several limitations suggested for the present study results. The database EMBASE was not included in the literature search, as the research team did not have free access to this electronic resource; since achievement of a comprehensive literature search is a prerequisite of systematic reviews, additional sources were explored manually. Further, the funnel plots point to possible publication bias. It is possible that other smaller, relevant studies that failed to prove an effect for psychological interventions simply have not been published. The present findings are also limited by the fact that only 12 randomized controlled trials were found as a result of the literature search versus 9 studies that employed a non-randomized method of allocation. There was considerable heterogeneity between studies with respect to certain outcomes. The heterogeneity of the Zhen *et al.* (2005) might be explained by its very specific study sample (insomnia patients with secondary infertility) and possible hidden methodological problems (suggested by its 100% return rate out of more than 506 patients). The studies also differed strongly with respect to the time point at which assessment occurred, ranging from 4 weeks to 6 months post-intervention. The present study does not provide any information on whether patients differing in cause and duration of infertility may benefit more or less from psychological interventions. Several of the effects discussed were only non-significant trends (e.g. greater benefits in women or in infertile patients not receiving ART) and therefore not that reliable. As a result, there is an urgent need for more and controlled evaluation studies. The results of the present meta-analysis can only provide answers regarding the average efficacy of psychological interventions for infertile patients with respect to mental health and pregnancy rates.

Recommendations for future research

The present meta-analysis investigated the efficacy of psychological interventions for infertile patients in connection with their mental health and pregnancy rates. One explanation for the small overall ES of such interventions on psychological outcomes could be the fact that infertile patients do not receive individualized psychological interventions. This lack of differentiated indication of psychological interventions to specific patients may lower the effects of the treatment (Roth and Fonagy, 2004). Future research should vary the specific objectives of different types of psychological interventions, namely the setting (single, couple or group), the type (e.g. psychotherapy, counselling and education) and the intensity (frequency and duration) of the intervention in randomized trials. Further, gender and the level of mental distress are important covariates in observational studies when trying to arrive at conclusions regarding the differential effect of psychological treatments in specific populations. Study results are still inconclusive regarding the best setting for psychological interventions aimed at infertile patients. Although De Liz and Strauss (2005) have found group and individual/couple interventions to be similarly effective, Boivin (2003) reports of group interventions being more effective. Future research should also further examine the gender-specific effects of psychological interventions for infertile patients. To date, the effect of including women's partners in treatment has not been adequately examined. Women and men ought to be analysed separately as there appear to be important differences in their processing of fertility-related information. Further, infertility patients' level of mental distress often varies according to the phase of infertility in which they find themselves. Therefore, patients' phase of infertility must also be taken into account. While there are several relevant notions of mental distress used in the literature (mental distress, distress caused by infertility, infertility-specific distress), there is still no clear accepted definition of mental distress used in connection with infertility. Adequate measures for infertility-specific mental distress (e.g. the intensity of one's wish for a child, cognitions about infertility) must be established in order to meaningfully examine the efficacy of relevant psychological interventions. Additionally, the dose–response relationship needs to be assessed further by focusing on the duration and intensity of psychological interventions. Overall, there are methodological flaws present in some primary studies. It is imperative that future research studies employ high-quality research design and that their results be presented in a clear, unequivocal manner in order to achieve more definitive conclusions regarding the efficacy of psychological interventions for infertile patients.

Clinical implications

Psychological interventions should be integrated in the treatment of infertility as the present study indicates that psychological interventions are somewhat effective in increasing pregnancy rates. However, with respect to mental health, the efficacy of psychological interventions for infertile patients could not be verified. Nevertheless, the present study provides some hints that psychological interventions which last longer—i.e. interventions with a duration of six or more sessions—may have a greater effect on infertile patients' mental health and

pregnancy rates. Finally, the present study indicates that psychological interventions are effective in increasing the pregnancy rates in particular among patients not receiving ART.

Conclusions

The findings of the present study provide some evidence in support of integrating psychological interventions as an early treatment strategy for infertile patients. Psychological interventions appear to increase infertile women's chances of becoming pregnant—in particular those who are not receiving ART. On the basis of the results, psychological interventions are beneficial for infertile patients, but more randomized controlled trials are needed.

Supplementary data

Supplementary data are available at http://humupd.oxfordjournals.org.

Acknowledgements

The authors extend their deepest thanks to all the researchers who provided them with additional information on their studies. The authors also wish to thank Anu Lannen, Martin Grosse Holtforth, Matthias Berking, Sven Tholen and Michelle Cattin for their valuable comments on earlier versions of the manuscript.

Conflict of interest: none declared.

Funding

The present study was supported by a grant from the Swiss National Science Foundation (grant no. 325100-11375411).

References

*References marked with an asterisk were included as controlled studies in the meta-analysis. °References marked with a point were excluded as uncontrolled studies or excluded controlled studies of the meta-analysis.

Abbey A, Halman LJ, Andrews FM. Psychosocial treatment and demographic predictors of the stress associated with infertility. *Fertil Steril* 1992;**57**:122–128.

Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *Br Med J* 2003;**326**:219.

Beaurepaire J, Jones M, Thiering P, Saunders D, Tennant C. Psychosocial adjustment to infertility and its treatment: male and female responses at different stages of IVF/ET treatment. *J Psychosom Res* 1994; **38**:229–240.

°Bents H. Verhaltenstherapeutische Paartherapie bei Kinderwunschpatienten. In: Brähler E, Myer A (eds). *Psychologische Probleme in der Reproduktionsmedizin. Jahrbuch der Medizinischen Psychologie*, Vol. **5**. Berlin: Springer, 1991, 144–155.

Boivin J. A review of psychosocial interventions in infertility. *Soc Sci Med* 2003;**57**:2325–2341.

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

°Brandt KH, Zech H. Effects of short-term psychotherapy on the success of an in vitro fertilization/embryo transfer program. *Wien Med Wochenschr* 1991;**141**:17–19.

°Brandt K, Zech H. Results of a prognosis study of in vitro fertilization after brief psychotherapy. *Geburtshilfe Frauenheilkd* 1992;**52**:297–300.

°Bresnick ER. A holistic approach to the treatment of the crisis of infertility. *J Marital Fam Ther* 1981;**7**:181–188.

°Bresnick E, Taymor ML. The role of counseling in infertility. *Fertil Steril* 1979;**32**:154–156.

Brkovich AM, Fisher WA. Psychological distress and infertility: forty years of research. *J Psychosom Obstet Gynaecol* 1998;**19**:218–228.

*Chan CHY, Ng EHY, Chan CLW, Ho PC, Chan THY. Effectiveness of psychosocial group intervention for reducing anxiety in women undergoing in vitro fertilization: a randomized controlled study. *Fertil Steril* 2006;**85**:339–346.

Chen TH, Chang SP, Tsai CF, Juang KD. Prevalence of depressive and anxiety disorders in assisted reproductive technique clinic. *Hum Reprod* 2004;**17**:2313–2318.

°Christie G, Morgan A. Individual and group psychotherapy with infertile couples. *Int J Group Psychother* 2000;**50**:237–250.

°Christie G, Morgan A. Individual therapy, group therapy and co-therapy work with infertile couples. *Aust J Psychother* 2006;**25**:83–103.

°Clark AM, Ledger W, Galletly C, Tomlinson L, Blaney F, Wang X, Norman RJ. Weight loss results in significant improvement in pregnancy and ovulation rates in anovulatory obese women. *Hum Reprod* 1995;**10**:2705–2712.

°Clark AM, Thornley B, Tomlinson L, Galletley C, Norman RJ. Weight loss in obese infertile women results in improvement in reproductive outcome for all forms of fertility treatment. *Hum Reprod* 1998; **13**:1502–1505.

Cochrane Collaboration: Review Manager 5.0. www.cc-ims.net/RevMan (4 September 2007, date last accessed).

Cohen J. *Statistical Power Analysis for the Behavioral Sciences*, revised edn. New York: Academic Press, 1977.

°Connolly KJ, Edelmann RJ, Bartlett H, Cooke ID, Lenton E, Pike S. An evaluation of counselling for couples undergoing treatment for in-vitro fertilization. *Hum Reprod* 1993;**8**:1332–1338.

°Cousineau TM, Corsini EA, Green TC, Barnard MT, Seibring A. A randomized-controlled study of an online infertility psychoeducational program. In: *Abstracts of the 62nd Annual meeting of the ASRM, New Orleans, LA, 2006* Abstract O-130. *Fertil Steril*.

Covington S, Burns LH. *Infertility Counseling: A Comprehensive Handbook for Clinicians*, 2nd edn. New York, NY: Cambridge University Press, 2006.

*De Klerk C, Hunfeld JAM, Duivenvoorden HJ, den Outer MA, Fauser B, Passchier J, Macklon NS. Effectiveness of a psychosocial counselling intervention for first-time IVF couples: a randomized controlled trial. *Hum Reprod* 2005;**20**:1333–1338.

De Liz TM, Strauss B. Differential efficacy of group and individual/couple psychotherapy with infertile patients. *Hum Reprod* 2005;**20**:1324–1332.

Demyttenaere K, Nijs P, Evers-Kiebooms G, Koninckx PR. Coping and the ineffectiveness of coping influence the outcome of in vitro fertilization through stress responses. *Psychoneuroendocrinology* 1992;**17**:655–665.

Demyttenaere K, Bonte L, Gheldof M, Vervaeke M, Meuleman C, Vanderschuerem D, D'Hooghe T. Coping style and depression level influence outcome in in vitro fertilization. *Fertil Steril* 1998; **69**:1026–1033.

°Domar AD, Seibel MM, Benson H. The mind/body program for infertility: a new behavioral treatment approach for women with infertility. *Fertil Steril* 1990;**53**:246–249.

°Domar AD, Zuttermeister PC, Seibel M, Benson H. Psychological improvement in infertile women after behavioral treatment: a replication. *Fertil Steril* 1992;**58**:144–147.

°Domar AD, Friedman R, Zuttermeister PC. Distress and conception in infertile women: a complementary approach. *J Am Med Womens Assoc* 1999;**54**:196–198.

*Domar AD, Clapp D, Slawsby E, Kessel B, Orav J, Freizinger M. The impact of group psychological interventions on distress in infertile women. *Health Psychol* 2000a;**19**:568–575.

*Domar AD, Clapp D, Slawsby EA, Dusek J, Kessel B, Freizinger M. Impact of group psychological interventions on pregnancy rates in infertile women. *Fertil Steril* 2000b;**73**:805–811.

Dunkel-Schetter C, Lobel M. Psychological reactions to infertility. In: Stanton AL, Dunkel-Schetter C (eds). *Infertility: Perspectives from Stress and Coping Research*. London, New York: Plenum Press, 1991, 29–57.

Dunkel-Schetter C, Stanton AL. Psychological adjustment to infertility. In: Stanton AL, Dunkel-Schetter C (eds). *Infertility: Perspectives from Stress and Coping Research*. London, New York: Plenum Press, 1991, 197–222.

Edelmann RJ, Humphrey M, Owens DJ. The meaning of parenthood and couples' reactions to male infertility. *Br J Med Psychol* 1994;**67**:291–299.

*Ellenberg J, Koren Z. Infertility and depression. *Int J Fertil* 1982; **27**:219–223.

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

*Emery M, Joris V, Béran M-D, Darwiche J, Capel R, Guex P, Germond M. Prospective study of pre-IVF counselling: one-year follow-up. *J Reprod Med Endocrinol* 2006;**1**:77–78.

Eugster A, Vingerhoets AJ. Psychological aspects of in vitro fertilization: a review. *Soc Sci Med* 1999;**48**:575–589.

Facchinetti F, Matteo ML, Artini GP, Volpe A, Genazzani AR. An increased vulnerability to stress is associated with poor outcome of in vitro fertilization-embryo transfer treatment. *Fertil Steril* 1997;**67**:309–314.

*Facchinetti F, Tarabusi M, Volpe A. Cognitive-behavioral treatment decreases cardiovascular and neuroendocrine reaction to stress in women waiting for assisted reproduction. *Psychoneuroendocrinology* 2004;**29**:132–173.

Freeman EW, Boxer AS, Rickels K *et al*. Psychological evaluation and support in a program of in vitro fertilization and embryo transfer. *Fertil Steril* 1985;**43**:48–53.

°Galletly C, Clark A, Tomlinson L, Blaney F. Improved pregnancy rates for obese, infertile women following a group treatment program: an open pilot study. *Gen Hosp Psychiatry* 1996a;**18**:192–195.

°Galletly C, Clark A, Tomlinson L, Blaney F. A group program for obese, infertile women: weight loss and improved psychological health. *J Psychosom Obstet Gynaecol* 1996b;**17**:125–128.

Gnoth C, Godehardt E, Frank-Herrmann P, Friol K, Tigges J, Freundl G. Definition and prevalence of subfertility and infertility. *Hum Reprod* 2005;**20**:1144–1147.

Greil AL. Infertility and psychological distress: a critical review of the literature. *Soc Sci Med* 1997;**45**:1679–1704.

Habbema JDF, Collins J, Leridon H, Evers JLh, Lunefeld B, te Velde ER. Towards less confusing terminology in reproductive medicine: a proposal. *Hum Reprod* 2004;**19**:1497–1501.

Harlow CR, Fahy UM, Talbot WM, Wardle PG, Hull MG. Stress and stress-related hormones during in-vitro fertilization treatment. *Hum Reprod* 1996;**11**:274–279.

Hauck WW. Odds ratio inference from stratified samples. *Commun Stat A-Theor* 1989;**18**:767–800.

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *Br Med J* 2003;**327**:557–560.

Hoffman BM, Papas RK, Chatkoff DK, Kerns RD. Meta-analysis of psychological interventions for chronic low back pain. *Health Psychol* 2007;**26**:1–9.

°Hölzle C, Brandt U, Lutkenhaus R, Wirtz M. Solution-focused counseling for involuntarily childless couples. In: Strauss B (ed). *Involuntary Childlessness: Psychological Assessment, Counseling, and Psychotherapy*. Ashland, OH: Hogrefe and Huber Publishers, 2002, 105–126.

Homan AC, Davies M, Norman R. The impact of lifestyle factors on reproductive performance in the general population and those undergoing infertility treatment: a review. *Hum Reprod Update* 2007; **11**:1–15.

Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of sample. *BMC Med Res Methodol* 2005;**5**:1–10.

°Kemeter P, Fiegl J. Das psychosomatisch orientierte Gespräch im Rahmen der Sterilitätsbehandlung - eine Quantifizierung der Gesprächsschwerpunkte und der therapeutischen Strategien. *J Fertil Reprod* 1999;**9**:23–31.

Klonoff-Cohen H. Female and male lifestyle habits and IVF: what is known and unknown. *Hum Reprod Update* 2005;**11**:179–203.

Klonoff-Cohen H, Chu E, Natarajan L, Sieber W. A prospective study of stress among women undergoing in vitro fertilization or gamete intrafallopian transfer. *Fertil Steril* 2001;**76**:675–687.

Leiblum SR, Greenfield DA. The course of infertility: immediate and long-term reactions. In: Leiblum S (ed). *Infertility: Psychological Issues and Counselling Strategies*. New York: John Wiley & Sons, 1997, 83–102.

Lespérance F, Frasure-Smith N, Koszycki D, Laliberté M-A, van Zyl LT, Baker B, Swenson JR, Ghatavi K, Abramson BL, Dorian P *et al*. Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease: the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial. *JAMA* 2007;**297**:367–379.

*Levitas E, Parmet A, Lunenfeld E, Bentov Y, Burstein E, Friger M, Potashnik G. Impact of hypnosis during embryo transfer on the outcome of in vitro fertilization-embryo transfer: a case–control study. *Fertil Steril* 2006;**85**:1404–1408.

Lipsey MW, Wilson DB. *Practical Meta-Analysis*. Thousand Oaks, CA: Sage, 2001.

*Liswood MP. Treating the crisis of infertility: a cognitive-behavioral approach. Dissertation Abstracts International Section A: Humanities and Social Sciences 55(12-A) 1995.

°McNaughton-Cassill ME, Bostwick JM, Vanscoy SE, Arthur NJ, Hickman TN, Robinson RD, Neal GS. Development of brief stress management support groups for couples undergoing in vitro fertilization treatment. *Fertil Steril* 2000;**74**:87–93.

*McNaughton-Cassill ME, Bostwick JM, Arthur NJ, Robinson RD, Neal GS. Efficacy of brief couples support groups developed to manage the stress of in vitro fertilization treatment. *Mayo Clin Proc* 2002;**77**:1060–1066.

*McQueeney DA, Stanton AL, Sigmon S. Efficacy of emotion-focused and problem-focused group therapies for women with fertility problems. *J Behav Med* 1997;**20**:313–331.

°Melamed RM, Bonetti TC, Pasqualotto FF, Locambo-Freitas CV, Iaconelli A, Borges E. Previous counseling to assisted reproduction treatment does bring the couples to reality. In: *Abstracts of the 61st Annual meeting of the ASRM, Montreal, Canada, 2005*. Abstract P-669. *Fertil Steril*.

Menning BE. The emotional needs of infertile couples. *Fertil Steril* 1980; **34**:313–319.

°O'Moore AM, O'Moore RR, Harrison RF, Murphy G, Carruthers ME. Psychosomatic aspects in idiopathic infertility: effects of treatment with autogenic training. *J Psychosom Res* 1983;**27**:145–151.

°Pengelly P, Inglis M, Cudmore L. Infertility: couples' experiences and the use of counselling in treatment centres. *Psychodyn Couns* 1995;**1**:507–524.

*Rezabek K, Vichova V, Pavelkova J, Zivny J. Hypnosis during embryo transfer does not ameliorate IVF results. In: *Abstracts of the 19th Annual Meeting of ESHRE, Madrid, Spain, 2003*. Abstract P-403. *Hum Repro*.

Rosenthal R, Rosnow RL, Rubin DB. *Contrasts and Effect Sizes in Behavioral Research: A Correlational Approach*. New York, NY: Cambridge University Press, 2000.

Roth A, Fonagy P. *What Works for Whom? A Critical Review of Psychotherapy Research*, 2nd edn. New York, NY: Guilford Press, 2004.

*Sarrel PM, DeCherney AH. Psychotherapeutic intervention for treatment of couples with secondary infertility. *Fertil Steril* 1985;**43**:897–900.

*Schmidt L, Tjornhoj-Thomsen T, Boivin J, Nyboe Andersen A. Evaluation of a communication and stress management training programme for infertile couples Patient. *Educ Couns* 2005;**59**:252–262.

*Shu-Hsin L. Effects of using a nursing crisis intervention program on psychosocial responses and coping strategies of infertile women during in vitro fertilization. *J Nurs Res* 2003;**11**:197–208.

Slade P, Emery J, Lieberman BA. A prospective, longitudinal study of emotions and relationships in in-vitro fertilization treatment. *Hum Reprod* 1997;**12**:183–190.

Smeenk JM, Verhaak CM, Eugster A, van Minnen A, Zielhuis GA, Braat DD. The effect of anxiety and depression on the outcome of in-vitro fertilization. *Hum Reprod* 2001;**16**:1420–1423.

Smeenk JM, Verhaak CM, Stolwijk AM, Kremer JA, Braat DD. Reasons for dropout in an in vitro fertilization/intracytoplasmic sperm injection program. *Fertil Steril* 2004;**81**:262–268.

Stanton AL, Tennen H, Affleck G, Mendola R. Cognitive appraisal and adjustment to infertility. *Women Health* 1991;**17**:1–15.

*Stewart DE, Boydell KM, McCarthy K, Swerdlyk S, Redmond C, Cohrs W. A prospective study of the effectiveness of brief professionally-led support groups for infertility patients. *Int J Psychiatry Med* 1992;**22**:173–182.

*Strauss B, Hepp U, Stading G, Mettler L. Focal counseling for women and couples with an unfulfilled desire for a child: a three-step model. In: Strauss B (ed). *Involuntary Childlessness: Psychological Assessment, Counseling, and Psychotherapy*. Ashland, OH: Hogrefe and Huber Publishers, 2002, 79–103.

Strauss B, Brähler E, Kentenich H. *Fertilitätsstörungen - psychosomatisch orientierte Diagnostik und Therapie*. Stuttgart: Schattauer, 2004.

°Takefman J, Brender W, Boivin J, Tulandi T. Sexual and emotional adjustment of couples undergoing infertility investigation and the effectiveness of preparatory information. *J Psychosom Obstet Gynaecol* 1990;**11**:275–290.

*Tarabusi M, Volpe A, Facchinetti E. Psychological group support attenuates distress of waiting in couples scheduled for assisted reproduction. *J Psychosom Obstet Gynaecol* 2004;**25**:273–279.

Thiering P, Beaurepaire J, Jones M, Saunders D, Tennant C. Mood state as a predictor of treatment outcome after in-vitro fertilization-embryo transfer technology (IVF/ET). *J Psychosom Res* 1993;**37**:481–491.

Tuschen-Caffier B, Florin I, Krause W, Pook M. Cognitive-behavioral therapy for idiopathic infertile couples. *Psychother Psychosom* 1999;**68**:15–21.

Verberg MFG, Eijkemans MJC, Heijnen EMEW, Broekmans FJ, de Klerk C, Fauser BCJM, Macklon NS. Why do couples drop-out from IVF treatment? A prospective cohort study. *Hum Reprod* 2008; **23**:2050–2055.

Visser AP, Haan G, Zalmstra H, Wouters I. Psychosocial aspects of in vitro fertilization. *J Psychosom Obstet Gynaecol* 1994;**15**:35–43.

Wilson DB. Effect size determination program. University of Maryland, College Park, 2001. http://mason.gmu.edu/~dwilsonb/ma.html.

Winkley K, Landau S, Eisler I, Ismail K. Psychological interventions to improve glycaemic control in patients with type 1 diabetes: systematic review and meta-analysis of randomised controlled trials. *Br Med J* 2006;**333**:65.

Wischmann T. Psychogenic infertility—myths and facts. *J Assist Reprod Genet* 2003;**20**:485–494.

Wischmann T. Psychosocial aspects of fertility disorders. *Urologe A* 2005; **44**:185–194.

*Wischmann T, Stammer H, Scherg H, Gerhard I, Strowitzki T, Verres R. Evaluation of the psychological effects of counselling and couple-therapy with infertile couples. Paper presented at the 17th Annual Meeting of the European Society for Human Reproduction and Embryology. *Hum Reprod* 2001a;**16**:198.

*Wischmann T, Stammer H, Scherg H, Gerhard I, Verres R. Psychological characteristics of infertile couples: a study of the "Heidelberg Fertility Consultation Service". *Hum Reprod* 2001b;**16**:1753–1761.

*Wischmann T, Stammer H, Scherg H, Gerhard I, Verres R. Couple counselling and therapy for the unfulfilled desire for a child: the two-step approach of the "Heidelberg Infertility Consultation". In: Strauss B (ed). *Involuntary Childlessness: Psychological Assessment, Counseling, and Psychotherapy*. Ashland, OH: Hogrefe and Huber Publishers, 2002, 127–150.

World Health Organization. The epidemiology of infertility: report of a WHO Scientific Group. WHO, Geneva, 1975.

World Health Organization. Current practices and controversies in assisted reproduction. Report of meeting on "Medical, Ethical and Social Aspects of Assisted Reproduction", 17–21 September 2001. WHO Headquarters, Geneva, Switzerland, 2002.

Wright J, Allard M, Lecours A, Sabourin S. Psychosocial distress and infertility: A review of controlled research. *Int J Fertil* 1989;**34**:126–142.

Wright J, Duchesne C, Sabourin S, Bissonnette F, Benoit J, Girard Y. Psychosocial distress and infertility: men and women respond differently. *Fertil Steril* 1991;**55**:100–108.

Zegers-Hochschild F, Nygren K-G, Adamson GD, de Mouzon J, Lancaster P, Mansour R, Sullivan E. The ICMART glossary on ART terminology. *Hum Reprod* 2006;**21**:1968–1970.

Zhen XH, Xie H, Xu X. Psychotherapy intervention for the insomnia status in patients with secondary infertility. *Zhongguo Linchuang Kangfu* 2005;**9**:33–35.

Submitted on January 9, 2008; resubmitted on December 16, 2008; accepted on January 3, 2009