

The effects of psychosocial interventions on the mental health, pregnancy rates, and marital function of infertile couples undergoing in vitro fertilization: a systematic review

Liyong Ying^{1,2} · Lai Har Wu¹ · Alice Yuen Loke¹

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Abstract

Purpose The purpose of this study was to examine the effects of psychosocial interventions on the mental health, pregnancy rates, and marital function of infertile couples undergoing in vitro fertilization (IVF), as determined through RCT studies. **Methods** Using the electronic databases PubMed, EMBase, Cochrane Library, CINAHL, PsycInfo, and CAJ, a systematic literature search was conducted in July 2015. MeSH terms, key words, and free words such as “infertility,” “fertilization in vitro,” “psychotherapy,” “intervention,” “anxiety,” “depression,” and “marital satisfaction” were used to identify all potential studies. The quality of the studies that were included was assessed using the risk of bias assessment tool developed by the Cochrane Back Review Group. Descriptive analysis was adopted to synthesize the results.

Capsule A complex intervention, based on sound evidence, should be developed targeting both females and males of infertile couples undergoing IVF treatment, particularly during the stressful period of waiting for the results of the pregnancy test result and after failed cycles.

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✉ Alice Yuen Loke
hsaloke@polyu.edu.hk

Liyong Ying
liying.ying@connect.polyu.hk

Lai Har Wu
candy.wu@polyu.edu.hk

¹ School of Nursing, The Hong Kong Polytechnic University, Hung Hom, Hong Kong, China

² School of Nursing, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, China

Results A total of 20 randomized controlled trials were included in this review. There were reports of positive effects on the anxiety levels, pregnancy rates, or marital function of infertile couples in six studies that adopted different psychosocial approaches, including mind body intervention (Eastern body-mind-spirit, Integrative body-mind-spirit, and Mind/body intervention), cognitive behavioral therapy, group psychotherapy, and harp therapy. However, there were methodological or practical issues related to measurement points and attrition rates in these studies. None of these interventions were found to be efficacious in relieving the depression or stress of individuals or couples undergoing IVF treatment. None of the included studies tackled or measured the mental health status of the couples during the most stressful time of waiting for the pregnancy results of their treatment. **Conclusions** A complex intervention, based on sound evidence, should be developed targeting both females and males of infertile couples undergoing IVF treatment, particularly during the stressful period of waiting for the results of the pregnancy test result and after failed cycles.

Keywords Infertile couples · In vitro fertilization · Mental health · Pregnancy rate · Psychosocial intervention · Systematic review

Background

It has been widely recognized that infertility affects a couple physically, emotionally, and socially [1]. When couples start seeking infertility treatments, there will be added suffering because of intrusive medical inquiries and procedures [2]. About 3 % of such couples will receive a recommendation to undergo assisted reproductive technologies (ARTs), and more than 99 % of these recommendations will be for in vitro fertilization (IVF)

[3]. Infertile couples usually resort to IVF treatment only after they have exhausted other options. Although IVF provides new hope to these couples, it also brings a great burden because of the low success rate of IVF, at 18.4–20.3 % (for frozen embryo transfer and fresh aspiration, respectively) [3].

In terms of the effects of infertility at the level of the individual, it has been reported that women undergoing IVF treatment experienced elevated levels of anxiety and depression during the pre-IVF treatment period, on the day of the retrieval of oocytes, during the transfer of embryos, and in the 2-week period of waiting for the results of the treatment [4–6]. The men of infertile couples also reported elevated levels of depression before the treatment and during the period of waiting for the results of the pregnancy test [7–9], although they were usually less involved or affected by the IVF cycle [9–11].

Studies have also explored the effects of the mental status of infertile couples on the outcome of their IVF treatments. Two systematic reviews with a meta-analysis of the predictive effects of psychological stress on the outcome of IVF treatments were inconclusive [12, 13]. In the first review, 31 prospective studies from 1978 to 2010 involving a total of 4902 participants were examined. It was concluded that there were small but significant associations between pre-treatment stress/distress and reduced pregnancy outcomes [12]. The other review of 14 prospective studies from 1985 to 2010 involving a total of 3583 infertile women found no association between pre-treatment anxiety or depression and the pregnancy outcomes of IVF treatment [13]. Nevertheless, the relationship between psychological stress and the pregnancy outcomes of IVF treatment deserves further exploration.

With regard to the effects of infertility at the couple level, studies have revealed that infertile couples have lower levels of marital satisfaction [14, 15]. Specifically, couples undergoing IVF reported much poorer marital quality than did fertile couples [5]. A study reported that regulars (couples who had received treatment for infertility for more than two but less than 5 years) and persisters (couples who had undergone treatment for 5 or more years) were less happy with their marriage than beginners (couples in the first 2 years of treatment) [16]. It was also reported that there were significant differences among infertile couples in different stages of medical treatment with regard to psychological distress and marital stress, including couples in the phases of pre-diagnosis, beginning treatment, receiving regular treatments, persisting in treatment, and concluding the treatment [14].

Reviews of psychological interventions

A variety of psychosocial interventions have been conducted for infertile women/couples receiving IVF treatment in an attempt to improve their mental health, pregnancy rates, and marital function. Four systematic reviews were conducted in 2003, 2005, 2009, and 2015 to examine the effects of various psychosocial interventions on infertile patients undergoing

fertility treatments [17–20]. The four reviews included studies targeting infertile patients across different stages of infertility treatments, from first-line treatments to ARTs. The four reviews also included non-randomized controlled trials, and three of the reviews included studies with no comparison groups [17, 18, 20]. The conclusions derived from these reviews were inconsistent. The two more recent reviews reported contradictory results on the effects of interventions on emotional distress and pregnancy outcomes, but both reported some effects, although non-significant, on interpersonal or marital function [19, 20].

As RCT is the gold standard of research, allowing one to ascertain that results of a study are due to the intervention [21], the shortcoming of these reviews was their inclusion of non-RCT studies. Thus far, there has not been a review focusing exclusively on RCT studies in exploring the efficacy of psychosocial interventions on patients/couples undergoing IVF treatment.

The purpose of the present review is to examine the effects of RCT studies of psychosocial interventions on the mental health, pregnancy rates, and marital function of patients/couples undergoing IVF. The findings of this review may provide healthcare professionals and researchers with information on the effectiveness and effect size of psychosocial interventions and on the implications for clinical practice and future research studies. The results will also inform the direction of the development of an intervention aimed at improving the experiences of infertile couples when undergoing IVF treatment.

Methods

Literature search strategy

Using the electronic databases PubMed (1966+), EMBase (1974+), Cochrane Library (1968+), CINAHL (1982+), PsycInfo (1806+), and CAJ (China Academic Journal Full-text Database, 1915+), a systematic literature search was conducted in the second week of July 2015. No language or time restrictions were set for this search. MeSH terms, key words, and free words such as “infertility,” “fertilization in vitro,” “sperm injections,” “intracytoplasmic,” “psychotherapy,” “intervention,” “program,” “anxiety,” “depression,” “pregnancy rate,” “marital relationship,” and “marital function” were used to identify potential studies. The full search histories were listed in Supporting Information Table S1. The references of the articles selected for review, and other related systematic reviews were also screened to further check for relevant articles.

Selection of studies for review and inclusion and exclusion criteria

The comprehensive literature search yielded a total of 1613 citations, with three additional records identified through a

hand search. After duplicate entries were removed, 1182 articles remained. The abstracts of these publications were screened, and 1130 papers that did not meet the inclusion criteria were excluded. The remaining 52 articles were further assessed for eligibility.

The criteria for studies to be included in this review were the following: the use of randomized controlled trials (RCT); a target population of infertile patients/couples planning to undergo/undergoing IVF/intracytoplasmic sperm injection (ICSI) treatment who had received a psychosocial intervention; and published in English or Chinese in a peer-reviewed journal. The articles published in Chinese must be included in the Chinese Science Citation Database (CSCD). In this review, psychosocial interventions refer to any intervention that focuses on psychological or social factors rather than biological factors [22]. The criteria for exclusion were as follows: studies involving patients undergoing intrauterine sperm insemination; studies that do not provide detailed information on the duration and number of sessions of interventions; and studies that were published in conference supplements or proceedings.

A total of 32 were excluded for the following reasons: not a psychosocial intervention study ($n=3$), a report of a study protocol only ($n=2$), published in conference supplements or proceedings ($n=4$), published in a language other than English or Chinese (Iranian, $n=2$), not involving RCTs ($n=12$), not targeted at infertile patients/couples undergoing IVF ($n=4$), a repeated report on the same population as that of another study ($n=3$), and no full text of the study available ($n=2$). As a result, a total of 20 RCT studies on psychosocial interventions for patients/couples who underwent IVF were included in this review. The selection procedures for this study are presented in Fig. 1.

Assessment of the quality of the reviewed papers

The quality of these studies was assessed using the risk of bias assessment tool developed by the Cochrane Back Review Group [23]. The tool consists of 12 items, presented in Supporting Information Table S2. Each item can be evaluated as “yes,” “no,” or “unsure,” with “yes” referring to a low risk of bias [23]. A study can be regarded as being of “a low risk of bias” when six or more items are rated as “yes” and no fatal flaws are identified [23]. In this review, two reviewers independently assessed the quality of the studies according to the appraisal checklist.

Data extraction

The following key components of the included studies were extracted and tabulated by the same two reviewers: (1) general information: first author, year of publication, and country of origin; (2) number of couples, males or females; (3) characteristics of the intervention: types, timing, numbers and

duration of sessions, duration of intervention, format, persons responsible for delivery, and measurement points; and (4) the efficacy of the interventions (outcome measures): anxiety, depression, stress, other psychosocial findings, and pregnancy rate (Table 1). In the case of significant results, estimates of effect size (Cohen’s d) are presented. The senior corresponding author met with the two reviewers to resolve any disagreements between the latter. Descriptive analysis was adopted to synthesize the results.

Results

General information of the studies

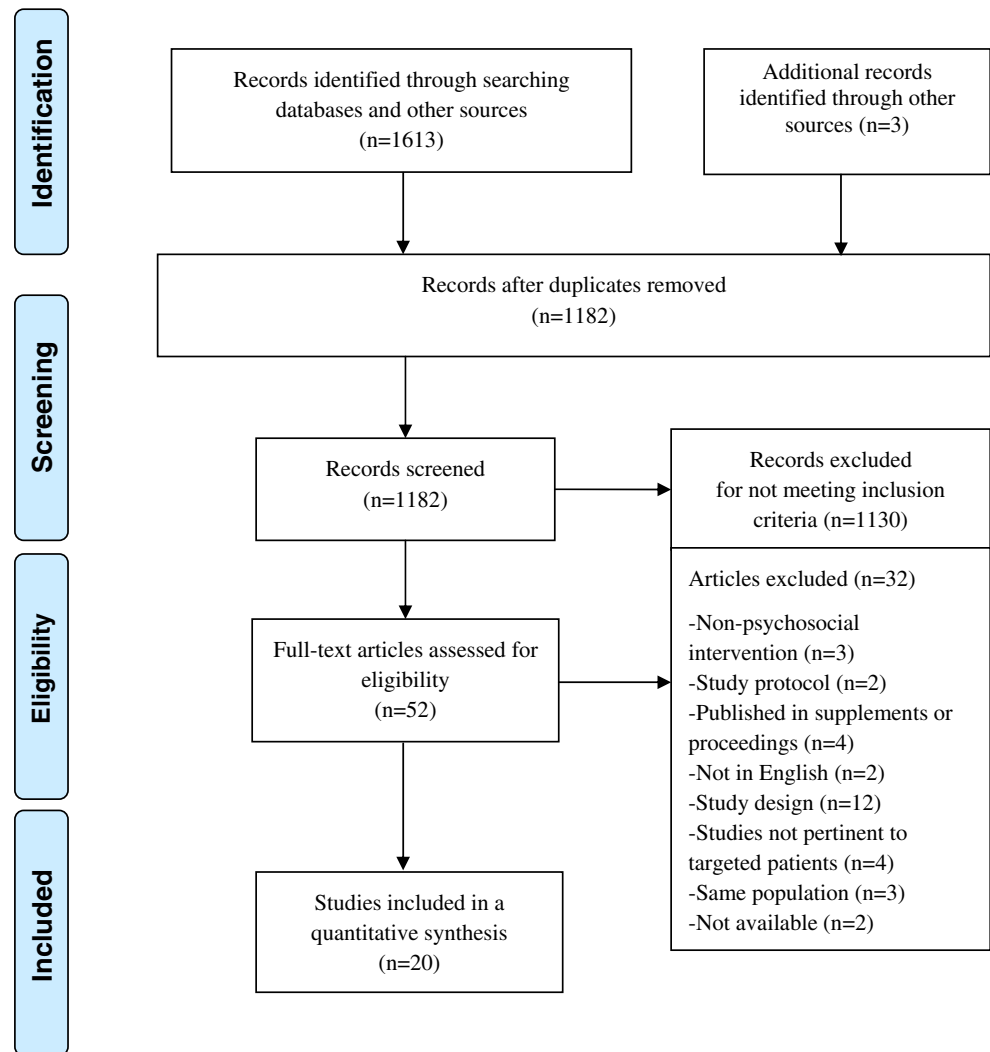
The 20 studies included in this review were published between 1993 and 2014 and conducted in 14 different countries or regions. Half of the studies had been conducted in Europe ($n=10$): including the Netherlands ($n=3$), UK ($n=2$), Denmark ($n=1$), France ($n=1$), Greece ($n=1$), Italy ($n=1$), and Switzerland ($n=1$); five in Asia: Hong Kong ($n=2$), Mainland China ($n=1$), Taiwan ($n=1$), and Iran ($n=1$); and the others in the USA ($n=3$), Brazil ($n=1$), and South Africa ($n=1$). Among the 20 studies that were included, only the study conducted in Mainland China had been published in Chinese [43].

Characteristics of the participants

Five studies focused on infertile couples as dyads, with an average sample size of 113 couples (range, 40–200) and a mean age of 32.9 years (32.0–34.4 years old). Fourteen studies focused on women of infertile couples, with a mean sample of 144 (range, 31–377) and a mean age of 33.7 (30.3–36.0), with the women in the study from Hong Kong being the oldest, at a mean age of 36.0 years [27]. The 14 studies also provided information on the duration of the diagnosis of infertility, ranging from 1.5 to 6.2 years (mean, 3.92 years). One focused on individual women or men of infertile couples, with a total of 82 participants, with a mean age of 33.17 years (range, 23–43) [39].

Methodological quality and risk of bias of the included studies

The outcomes of the quality assessment for the 20 RCT studies are presented in Supporting Information Table S2. The methodological quality of these studies was reasonably good. All but one of the studies met at least six criteria and were considered as being of “low risk of bias” according to the Cochrane assessment tool [23]. The one study with five items in the appraisal checklist that were rated “yes,” conducted by Connolly et al. in the UK [30], was the only study that had

Fig. 1 Literature search and study selection

been published in the 1990s, but it met the criteria for inclusion.

The method of randomization was adequately described in 12 studies. The concealment of the allocation was appropriately described in nine studies. Due to the nature of the intervention, the blinding of the participants, care providers, and outcome assessors was only adopted in five, four, and seven studies, respectively.

The dropout rate was described and deemed to be acceptable in 13 of the included studies. The reasons for refusing to participate in the study or for dropping out included the following: medical reasons (poor treatment response, zero embryos transferred, or treatment cancellation), no need for further counseling, excessive time commitment, dislike of study tasks, financial considerations, and spontaneous pregnancy or adoption. Only five studies reported that all of the participants randomized in trials had been analyzed by intention to treat. No trial was suggestive of selective outcome reporting. All of the studies reported similarities between the intervention and control groups in baseline characteristics. The majority of the

studies (19 studies) mentioned that co-interventions or similar interventions were avoided. The compliance of the participants was acceptable in 14 studies. All of the trials reported a similar timing between the groups in the measurement of outcomes.

Characteristics of the interventions

A total of 14 different types of interventions were adopted in the 20 RCT studies included in this review. They can be classified into five categories: cognitive behavioral therapy (CBT) ($n=3$), mind-body intervention (MBI) ($n=3$), counseling ($n=4$), positive reappraisal coping therapy ($n=2$), and other psychosocial interventions ($n=8$). These other psychological interventions included hypnosis, Internet-based interventions, crisis interventions, expressive writing, harp therapy, written emotional disclosure, telephone emotional support, and group psychotherapy. The interventions were conducted at different time-points in the IVF treatment cycle, including six studies at the wait-listed period, two during embryo transfer, four at the

Table 1 Characteristics and outcomes of psychosocial interventions for patients undergoing IVF treatment

Reference, country	Participants (N)		Intervention name (category)	Timing	Number of sessions	Format	Delivery person	Measurement points	Outcomes				
	Intervention	Control							Anxiety	Depression	Stress	Pregnancy rate	Other psychological outcomes
Corayeb et al. [24] Brazil	93 C	95 C	Brief cognitive behavior intervention (CBT)	Before cycle	5 sessions 2 h 5 weeks	Group/couple Face to face	Psychologist	Post-test (the end of the cycle)	-	-	-	(†): $d = 0.43$	-
Mosalanejad et al. [25] Iran	15 F	16 F	Cognitive behavioral therapy (CBT)	Before cycle	15 sessions 1.5 h 4 months	Group/female Face to face	Psychologist	Pre-test (referring to the ART clinic), Post-test (4 months later)	(‡): $d = 0.95$, within group	(‡): $d = 1.64$, within group	(‡): $d = 1.92$, within group	-	Hardiness (†): $d = 4.99$
Tarabusi et al. [26] Italy	28 C	28 C	Cognitive behavioral treatment (CBT)	Before cycle	12 sessions 1 hour 4 months	Group/couple Face to face	Psychologist	Pre-test (being scheduled for IVF/ICSI), Post-test (4 months later)	(-)	(-)	(-)	(-)	Psychological uneasiness of female (‡): $d = 0.260$, within group
Chan et al. [27] Hong Kong	69 F	115 F	Eastern body-mind-spirit (MBI)	Before cycle	4 sessions 3 h 4 weeks	Group/female Face to face	Practitioner	Pre-test (referring to the ART center), Post-test (the day of the start of ovarian stimulations), Follow-up (the day of ET, 1 month later)	(‡): state anxiety ^a (-): trait anxiety	-	-	(-)	Importance of childbearing (self) (‡) ^b Importance of childbearing (marriage) (-)
Chan et al. [28] Hong Kong	172 F	167 F	Integrative body-mind-spirit (MBI)	Before cycle	4 sessions 3 h 4 weeks	Group/female Face to face	Practitioner	Pre-test (referring to the ART center), Post-test (the day of the start of ovarian stimulations), Follow-up (the day of ET, 1 month after the post-test)	(‡): state anxiety, Post-test: $d = 0.59$; follow-up: $d = 0.46$; (‡)trait anxiety, Post-test: $d = 0.29$; follow-up: $d = 0.29$	-	-	(-)	Marital satisfaction: post-test (-); follow-up (†): $d = 0.29$ Importance of childbearing (‡): post-test: $d = 0.41$; follow-up: $d = 0.59$ Negative affect: post-test (-); follow-up (‡): $d = 0.35$ Positive affect: post-test (-); follow-up (†): $d = 0.20$
Domar et al. [29] USA	46 F	51 F	Mind/body intervention (MBI)	During cycle	10 sessions 2 h 10 weeks	Group/female Face to face	Practitioner	Post-test (the end of each cycle)	-	-	-	(†): $d = 0.82$,	-
Connolly et al. [30] UK	37 C	45 C	Counseling	During cycle	3 sessions 1 h 3 weeks	Dyadic couple Face to face	Counselor	Pre-test (first visit to the clinic), beginning of the treatment cycle, Post-test (at the end of the treatment cycle)	(-)	(-)	(-)	(-)	General psychological state (-) Self-esteem (-) Mood state (-)
de Klerk et al. [31] The Netherlands	21 C	19 C	Counseling	During cycle	3 sessions 1 h 4 weeks	Dyadic couple Face to face	Social worker	Pre-test (1 week before the down-regulation or the first day of the pruitary down-regulation), Post-test (2 weeks after the pregnancy)	(-)	(-)	(-)	(-)	Distress (-)

Table 1 (continued)

Reference, country	Participants (N)		Intervention name (category)	Timing	Number of sessions	Duration of each session	Format	Delivery person	Measurement points	Outcomes					
	Intervention	Control								Anxiety	Depression	Stress	Pregnancy rate	Other psychological outcomes	
Emery et al. [32] Switzerland	100 C	100 C	Counseling	Before cycle	1	1–1.5 h 1 day	Dyadic couple Face to face	Counselor	Pre-test (before the start of IVF), Post-test (6 weeks after ET)	(-)	(-)	(-)	(-)	(-)	(-)
Zyl et al. [33] South Africa	25 F	27 F	Counseling	During cycle	2	Unclear 5–10 days	Individual/ female Face to face	Embryologist	Pre-test (days 4–9 of the menstrual cycle), Post-test (after oocyte aspiration)	(-)	(-)	(-)	(-)	(-)	Use of problem-focused coping strategies (↑): $d = 0.35$, within group
Lancastle et al. [34] UK	28 F	27 F	Positive reappraisal coping intervention (coping therapy)	During 2-week waiting period	28	1 min 14 days	Individual/ female; Self-administered	Patient herself	Pre-test (the day of embryo transfer), Post-test (the day of the pregnancy test)	(-)	(-)	(-)	(-)	(-)	Dispositional optimism (↑): Helpfulness: $d = 0.69$ Suitability: $d = 0.71$ Confidence: $d = 0.66$ Enduring effects: $d = 0.71$ Feeling positive: $d = 0.83$ Future plans: $d = 0.73$ Sustained coping: $d = 0.70$
Ockhuijsen et al. [35] The Netherlands	127 F	126 F 124 F	Positive reappraisal coping intervention (coping therapy)	During 2-week waiting period	28	1 min 14 days	Individual/ female; Self-administered	Patient herself	Pre-test (before the waiting period), Post-test (on day 10 of the 14-day waiting period), Follow-up (6 weeks after the start of the waiting period)	(-)	(-)	(-)	(-)	(-)	Daily negative emotions (-) Positive emotions (↑) ^b : (group by time interaction: $F(1, 2652) = 16.15$)
Catoire et al. [36] France	50 F	43 F	Hypnosis (others)	During embryo transfer	1	20–30 min	Individual/ female; Face to face	Hypnotist	Pre-test (before the embryo transfer), Post-test (after ET)	(-)	(-)	(-)	(-)	(-)	(-)
Tuul et al. [37] The Netherlands	51 F	40 F	Internet-based record (others)	During cycle	Infinite	Infinite	Dyadic couple; via Internet	Couple themselves	Pre-test (before cycle), Post-test (the end of the cycle)	(-)	(-)	(-)	(-)	(-)	Patient empowerment (-)
Lee et al. [38] Taiwan	64 F	68 F	Nursing Crisis Intervention Program (others)	During cycle	2 videos and 3–6 phone counseling Video: 30–40 min; counseling: unclear	The period of a cycle	Individual/ female; via video and phone	Counselor	Pre-test (the initial stage of treatment-day 3), Middle (at the stage of the embryo transfer), Post-test (before the pregnancy test)	(-)	(-)	(-)	(-)	(-)	Psychological responses (-) Coping strategies (-)

Table 1 (continued)

Reference, country	Participants (N)		Intervention name (category)	Timing	Number of sessions	Duration of each session	Format	Delivery person	Measurement points	Outcomes				
	Intervention	Control								Anxiety	Depression	Stress	Pregnancy rate	Other psychological outcomes
Mathiesen et al. [39] Denmark	42 (F + M)	40 (F + M)	Expressive writing intervention (others)	2 weeks after the start of the cycle	3 20 min 3 days		Individual/female or male; self-administered	Patient themselves	Pre-test (at treatment enrollment), Post-test (3 weeks later), follow-up (6 weeks after the intervention)	-	-	(↓): $d = 0.46$, within group	-	-
Murphy et al. [40] USA	90 F	91 F	Harp therapy (others)	During embryo transfer	1 20 min 20 min		Individual/female; face to face	Music practitioner	Pre-test (before the embryo transfer), Post-test (after ET)	(↓): state anxiety, $d = 0.457$	-	-	(-)	-
Panagopoulou et al. [41] Greece	50 F	50 F 48 F	Written emotional disclosure (others)	During 2-week waiting period	7 20 min 1 week		Individual/female; self-administered	Patient herself	Pre-test (2 h after ET), Post-test (2 days prior to the pregnancy test)	(-)	-	(-)	(-)	Positive and negative affect (-) Infertility-related concerns (-)
Skias et al. [42] USA	66 F	65 F	Emotional support-phone call (others)	During 2-week waiting period	2 5–15 min 2 weeks		Individual/female; via phone	Social workers	Pre-test (the day of ET), Post-test (10 days after ET)	-	-	(-)	-	-
Zhu et al. [43] China	50 F	50 F	Group psychotherapy (Others)	During cycle	6 1.5–2 h 3 weeks		Group/female; face to face	Psycho-therapist	Pre-test (the initial stage of treatment days 3–4), Post-test (the end of the intervention)	(↓): $d = 0.46$	(-)	(-)	(-)	(-)

C couple, F female, M male, CBT cognitive behavioral therapy, MBI mind-body intervention

^a No standard deviation provided

^b No mean and standard deviation provided

2-week waiting period before the pregnancy test, and eight throughout the whole treatment cycle.

The number and duration of the sessions for each intervention varied. For CBT, the number of sessions ranged from 5 to 15 (mean 10.7 sessions) over 5 weeks to 4 months, with each session lasting for 1 to 2 h per session. MBI ranged from four to ten sessions (mean six sessions), with 2 to 3 h per session and over 4 to 10 weeks. Counseling ranged from one to three sessions (mean 2.3 sessions), and each session lasted for 1 to 1.5 h for 1 to 28 days. Coping therapy was by means of reading cards for at least twice a day for 14 days. Disparities in terms of numbers and duration of sessions were also seen in the other psychosocial interventions also showed (details are given in Table 1).

Most of the interventions were delivered face to face ($n=13$). The rest were self-administered activities (expressive writing, $n=2$; reading cards, $n=2$), emotional support through telephone and video viewing ($n=2$), or delivered through the Internet ($n=1$). The 13 face-to-face interventions included females in a group intervention ($n=5$), females on an individual basis ($n=3$), couples in dyads ($n=3$), and couples in a group intervention ($n=2$). Apart from the five self-administered or internet-based interventions, the 15 interventions were delivered by psychologists ($n=4$), practitioners trained in MBI ($n=3$), music therapists ($n=1$), counselors ($n=3$), social workers ($n=2$), embryologists ($n=1$), and hypnotists ($n=1$).

Intervention components

The main components of the psychosocial interventions included in the 20 studies were psycho-education, skill training, emotional support, and cognitive restructuring (Table S3).

The psycho-education refers to the provision of information about medical treatments and the reciprocal influence between physical and psychological status. Five intervention studies included a psycho-educational element [24, 26, 37, 38, 43], although in other studies this is usually conveyed as routine care. Training in a variety of skills was provided, including instruction in stress reduction techniques [25, 27, 28], relaxation techniques and exercise [24, 25, 27–29, 38, 43], communication skills [25, 43], coping strategies [34, 35], and problem-solving techniques [25]. The emotional support that was employed mainly focused on emotional expression and sharing. Participants were encouraged to talk or write down their feelings, thoughts, expectations, or difficulties [30–33, 39, 41, 42], or share in groups [25, 26, 37, 43], and support was provided flexibly according to the needs of the patients [30–33, 37, 42, 43].

A total of five studies adopted cognitive restructuring to deter negative thoughts and to establish positive thoughts or beliefs [24–26, 29, 43]. Other components such as health behavior modification was also adopted in one intervention

study [29]. Other psychotherapies, such as hypnosis [36] and harp therapy [40], were used to improve the psychological status and clinical outcomes of IVF patients.

Efficacy of the interventions

A variety of outcomes were measured to evaluate the efficacy of the interventions, including anxiety, depression, stress, other psychological outcomes, pregnancy rates, and marital function. Among all, anxiety and depression were regarded as the two indicators most sensitive to the stress-induced activation of the hypothalamic-pituitary-adrenal axis [44].

Anxiety

Of the 20 RCTs, 15 examined the effects of interventions on the anxiety levels of infertile patients who had undergone IVF treatment. The anxiety levels of patients/couples were measured using the State-Trait Anxiety Inventory (STAI) [27, 28, 30, 32, 36–38, 40, 41, 43], the Hospital Anxiety and Depression Scale (HADS) [31, 35], the Beck Anxiety Inventory (BAI) [33], the short-form Depression Anxiety Stress Scale (DASS-21) [25], and the Symptom Rating Test (SRT) [26].

Only four RCT studies reported significant positive effects from the interventions when compared to the control group [27, 28, 40, 43]. All four of these studies were targeted at women. A study conducted in Hong Kong reported that women who had received a four-session, 3-h Integrative Body-Mind-Spirit intervention during the waiting period before the cycle had significantly lower levels of state anxiety on the day of ovarian stimulation (T1) and embryo transfer (T2) (state anxiety, T1 $d=0.59$, T2 $d=0.46$; trait anxiety, T1 $d=0.29$; T2 $d=0.29$) [28]. Similar findings were reported in another study conducted by the same authors that adopted an Eastern Body-Mind-Spirit intervention [27]. It is worth noting that both studies did not follow up on the effects of the intervention on anxiety levels at the period of pregnancy testing.

A study conducted in China indicated that women who attended a six-session, 3-week Group Psychotherapy program during IVF treatment reported experiencing lower levels of anxiety at the end of intervention ($d=0.46$) [43]. However, the time-point of post-test was not clearly reported. It is unclear whether the pregnancy results were disclosed at post-test [43]. Another study involving 180 American women undergoing embryo transfer revealed that the women had significant lower levels of state anxiety after a 20-min session of harp therapy ($d=0.457$). There was no effect on trait anxiety [40].

Apart from the above four studies, the effects on anxiety within the intervention group have been described in two studies in which CBT ($d=0.95$) and counseling ($d=0.34$) were adopted [25, 33]. Another study revealed that there was no significant difference between the effects of hypnosis

and diazepam on anxiety levels in women undergoing embryo transfer [36]. The remaining eight studies showed no effects on the anxiety levels of patients undergoing IVF treatment [26, 30–32, 35, 37, 38, 41].

In short, 4 out of 14 studies (28.6 %) showed a medium effect size (range, 0.46–0.59) on the level of state anxiety. However, none of these intervention studies examined anxiety levels during the 2-week waiting period for a pregnancy test, recognized as the most difficult period for infertile couples [4]. It is also important to note that men of infertile couples were not included in these intervention studies.

Depression

Nine of the 20 RCT studies measured the effects of interventions on depression. Depression was measured using the HADS [31, 35], Beck's Depressive Inventory (BDI) [32, 33], Zung's Self-Administered Depression Scale (Z-SDS) [38], the Self-Rating Depression Scale (SDS) [43], DASS-21 [25], the Profile of Mood States-Bipolar form (POMS) [30], and the SRT [26].

None of these nine studies showed that the interventions had significant effects on the depressive symptoms in IVF patients compared with those in the control group [25, 26, 30–33, 35, 38, 43]. One of these studies with a small sample size of 31 women reported that the 15-session CBT intervention lasting for 4 months had a demonstrated effect ($d=1.64$) on the depression level within the intervention group [25], although the difference between the intervention and control groups did not reach statistical significance.

Stress

Stress was measured in five RCT studies using the IVF stress inventory (SI) [30], the Fertility Problem Stress Scales (FPSS) [39], the short-form DASS-21 [25], the Infertility and Strain Scale (ISS) [41], and the Perceived Stress Scale (PSS) [42]. These studies explored the effect of interventions on the stress levels of patients undergoing IVF treatment [25, 30, 39, 41, 42], but in no study was a significant difference in stress level demonstrated between infertile patients in the intervention and control groups. Two of these studies adopting CBT and Expressive Writing Intervention showed positive effects (CBT, $d=1.92$; EW, $d=0.46$) on the stress level within the intervention group, while no significant difference was found when compared to control groups [25, 39]. It is worth noting that only 31 participants were analyzed in these two studies (intervention group, $n=15$, control group, $n=16$) [25, 39].

Other psychological outcomes

Apart from the above-mentioned outcomes that were measured, a total of 14 other psychological outcomes were

measured in the included studies. Four studies showed interventions that had positive effects on five different measures, including the decreased importance of childbearing (post-test, $d=0.41$; follow-up, $d=0.59$) [28], reduced negative affect (follow-up, $d=0.35$) [28], improved positive affect (follow-up, $d=0.20$; group by time interaction, $F[1,2652]=16.15$) [28, 35], enhanced hardiness ($d=4.99$) [25], and increased dispositional optimism (helpfulness, $d=0.69$; suitability, $d=0.71$; confidence, $d=0.66$; enduring effects, $d=0.71$; feeling positive, $d=0.83$; future plans, $d=0.73$; sustained coping, $d=0.70$) [34]. The interventions that were adopted were the Integrative Body-Mind-Spirit intervention [28], the Positive Reappraisal Coping intervention [34, 35], and CBT [25].

However, eight studies reported no significant differences between the intervention and control groups regarding 11 measured outcomes. These measures included negative affect [35, 41], positive affect [41], the use of coping strategies [33, 38], psychological uneasiness [26], general psychological state [30], self-esteem [30], mood state [30], distress [31], patient empowerment [37], psychological responses [38], and infertility-related concerns [41].

Pregnancy rates

Ten studies examined the effect of psychosocial interventions on the pregnancy outcome of women who had undergone IVF treatments. Only two studies reported positive effects [24, 29]. The study involving 188 couples found that after five sessions of brief CBT, the pregnancy rate was much higher ($d=0.43$) in the intervention than in the control group [24]. Another study using group MBI for infertile women before they had started their first IVF cycle indicated that the pregnancy rates of MBI participants were higher in the second IVF cycle ($d=0.82$) than those for the control group [29]. However, the high rates of attrition for the samples, 34 % for brief CBT and 32.2 % for MBI, might have affected the interpretation of the results in the two studies.

The other eight studies reported no significant difference in pregnancy rate between the intervention and control groups [27, 28, 35–37, 40, 41, 43]. Moreover, in one of these six studies, ironically the non-participants of the RCT study reported significantly higher pregnancy outcomes when compared with those participating in the written emotional disclosure intervention and those in the control group [41].

Although the differences between groups did not reach statistical significance, three of these eight studies [28, 37, 41] have been regarded as having positive and promising effects on pregnancy rates in a recent review [20]. The effect sizes of these interventions, including MBI, written emotional disclosure, and Internet-based intervention, have also been pooled using meta-analysis [20].

In summary, among the ten studies, only two (25 %) indicated significant effects on the pregnancy rate, with effect

sizes ranging from 0.43 to 0.82 (Cohen's d), by adopting brief CBT and MBI, respectively.

Marital function

Only 1 of the 20 RCTs included marital function as an outcome measure. Marital function was measured using the Kansas Marital Satisfaction Scale (KMS) [28]. The Integrative Body-Mind-Spirit intervention study indicated that women in the intervention group reported higher marital satisfaction than those in the control group at the 1-month follow-up (on the day starting ovarian stimulation) ($d=0.29$), while there was no significant effect at post-treatment [28]. The components of the intervention were thought to be responsible for such an outcome. They included group sharing about effective marital communication and discussions among the couples about their values and expectations of treatment. It should be noted that the men of these infertile couples were not recruited to take part in the study.

Overall effects of psychological interventions

It is concluded that, overall, these interventions had positive outcomes for patients undergoing IVF treatment, including improved anxiety, other psychological outcomes, pregnancy rates, and marital function. However, none of these interventions demonstrated positive effects on the anxiety and depression of patients or couples during the time that they were waiting for the pregnancy results of their treatment. More studies are needed to explore the evidence on the effects of these interventions on pregnancy outcomes and marital function. The other psychotherapies, including hypnotherapy and hypnosis, were effective in reducing anxiety levels specifically during the procedure of embryo transfer. Coping therapy could be used to enhance the positive effect during the waiting period before the pregnancy test.

Discussion

The results of this review indicate that CBT, MBI, counseling, and coping therapy are the most frequently adopted psychological interventions for infertile women and men of infertile couples. Generally speaking, no positive effects on outcome measures have been reported for simple counseling interventions. Coping therapy was found to be effective only in improving the positive emotions of couples. The approaches of CBT and MBI showed some positive effects on anxiety, pregnancy rates, or marital function in four studies. However, there were methodological or practical issues in these studies relating to measurement points and attrition rates that must be dealt with, before there can be any assurance about the effects of the psychosocial interventions.

The timing of outcome measures is one aspect that one should be cautious about when interpreting the results of these interventions. Two studies that adopted the MBI approach reported that it was effective at reducing anxiety at the start of the period of ovarian stimulation (post-test assessment) [27, 28], when patients usually exhibit only slightly higher anxiety than normal [4]. However, the 2-week waiting period for the pregnancy test, regarded as the most difficult time of the IVF treatment, was not examined [4]. There is similar concern about the effect of the intervention on the marital function of couples who were assessed on the day that the embryo was transferred [28]. At this time-point, couples have not yet received the result of the pregnancy test, which could be a challenge to the marital satisfaction of the couples. It is concluded that the effects of MBI on the anxiety and marital function of infertile couples during IVF treatment cannot be confirmed.

Another aspect to be cautious about when interpreting results is the high attrition rate in these intervention studies. Two studies reported that pregnancy rates were enhanced by adopting the brief CBT and MBI [24, 29]. However, only 70 % of couples had attended at least two out of five group sessions of CBT [24] and only 9 % of the participants had taken part in at least one half of the MBI sessions at the start of cycle 1 (76 % at cycle 2) [29]. One of the eight studies that examined pregnancy outcomes reported that the women who had refused to participate the study had a higher pregnancy outcome than those in the intervention and control groups [41]. No conclusion can be reached on the efficacy of CBT and MBI on pregnancy outcomes.

This review of studies revealed several areas in need of improvement in future psychological interventions for infertile couples, namely, the target sample, components, and timing of the interventions, the time-point of outcome measurements, and the therapists involved in the interventions.

First, supportive interventions should target infertile couples at the dyad level instead of at the individual level of men or women. A systematic review has revealed that couples who underwent IVF treatment suffered from the stressful experience as dyads [45]. Also, the depression score of men has been identified as an independent predictor of a reduced likelihood of clinical pregnancy [46]. However, 13 out of the 20 (65 %) RCT studies in this review neglected the men of infertile couples.

Second, interventions should include a component to enhance the marital function of the couples. Although the relationship between two partners and the support that they give to each other play an important role in the way that couples cope with IVF treatment [47], only one study in this review included the enhancement of marital satisfaction in the intervention [28]. All other intervention studies neglected this important aspect of couple support.

Third, a psychological intervention should also be provided to infertile women and men who have undergone IVF, after

the disclosure of a negative pregnancy result. Studies have reported that when IVF treatments are unsuccessful, heartbreak, shock, and psychological trauma can be long-lasting for the couples [40, 44]. However, none of the interventions in the included RCT studies provide support to ease the psychological distress of couples after the disclosure of a negative pregnancy result.

Fourth, the time-points for measuring outcomes of interventions should be carefully selected. None of the included studies measured the psychological outcomes of interventions during the hardest 2-week waiting period of IVF. Also, the outcome measured at the end of the treatment cycle could be affected by a positive pregnancy result. One of the studies included in this review reported that women had a lower level of anxiety at the end of the 3-week intervention [43]. However, at this time-point, some women might already have been informed of a positive result from their pregnancy test and therefore had a lower level of anxiety [48].

Lastly, as the professional group that closely cares for the couples throughout the IVF treatment, nurses should be aware of their responsibility to provide the psychological support that the infertile couples need. This review showed that none of the interventions in the included studies were delivered by nurses.

To conclude, the abovementioned issues need be addressed before the efficacy of interventions can be confirmed. Interventions should be developed to fill the gaps identified in this systematic review.

Similarities and differences of the findings of this and previous reviews

As mentioned, there were four reviews conducted previously prior to this review. However, the four included also studies on infertile patients across different stages of infertility treatments as well as non-randomized control trials or without comparison groups [17–20]. The conclusions of the four reviews were inconsistent.

The two reviews, published in 2003 (Boivin) and 2005 (de Liz and Strauss), reported of a beneficial effect of intervention on psychological distress, whereas the result in terms of pregnancy rates was equivocal [17, 18]. The review in 2003 derived the findings from eight controlled studies and concluded that there was no clear efficacy for pregnancy rates [17]. It was suggested that high-quality studies are needed in order to delineate specifically the effectiveness of psychosocial interventions [17].

The review published in 2009 was the only review that included controlled studies exclusively, but the efficacy of the psychosocial interventions for improving mental health in infertile patients or for increasing pregnancy rates for women receiving ART were not confirmed [19]. This was supported by the result of a meta-analysis of psychosocial studies that

pre-treatment emotional distress was not related to the outcome of ART treatment [13].

Inconsistent with three previous reviews, the most recent one published in 2015 reported positive efficacy of interventions in improving psychological distress and in increasing pregnancy chances of couples undergoing infertility treatment [20]. However, a closer look of the findings of the review revealed that there were no statistically significant effects of the interventions on the infertility stress and marital function of infertile couples. After adjusting for potential publication bias, no significant effects were found on the levels of depression and state anxiety for men and women. The effect size of pregnancy outcomes in RCTs was smaller than that in non-RCTs, while the possible moderating influence of medical treatment (e.g., IVF/ICSI versus no IVF/ICSI) has not been explored [20].

The findings of our present review also revealed that the effects of various interventions on the levels of depression, anxiety, stress, pregnancy rates, and marital function of infertile individuals/couples undergoing IVF treatment could not be confirmed, consistent with that reported in previous reviews.

Recommendations for future research

The findings of this systematic review provide directions and insights for healthcare professionals and researchers seeking to provide a supportive psychosocial intervention for couples undergoing IVF treatment. As there were no convincing outcomes in these studies to demonstrate the efficacies of the intervention approaches that were adopted, a new intervention should be developed.

Since IVF couples experience psychological stress in their marriage, it would be desirable to develop a complex intervention focusing on both the mental health and marital function of couples. In a concept analysis of “partnership” in the context of infertility, it has been revealed that couples can expect to achieve marital benefits and improvements in their psychological well-being [49]. A qualitative study among infertile couples also confirmed the importance of partnership and support for the psychological well-being of couples [47]. It is concluded that it is desirable to develop an intervention targeting females and males of infertile couples as dyads, and to integrate the enhancement of partnership in couples as a component in the intervention program.

Attention should be paid in the intervention to the two difficult periods for couples undergoing IVF treatments—the time spent waiting for the result of the treatment and after the disclosure of a negative result from the pregnancy test. Accordingly, the time-points for measuring outcomes should be on the day before the pregnancy test and after the disclosure of the result of the treatment (e.g., 1 month later), in order to exactly examine the effects of the intervention.

Clinical nurses working with infertile couples could be trained to conduct such psychosocial interventions. Once the efficacy of the program has been proven, it could be integrated into nursing routine care, which currently focuses merely on information education in general [47].

Also, the high attrition rates identified in the studies included in this review, which might have affected the reliability of the intervention results, should be addressed. Some possible strategies can be used to reduce attrition rates, such as communication, incentives, and assistants for establishing rapport.

Recommendations for clinical practice

This review provides some implications for healthcare providers who work with infertile couples undergoing IVF treatment. The studies indicated that psychotherapies such as harp therapy could be used to reduce anxiety, specifically during the procedure of embryo transfer. With respect to the dreaded 2-week period of waiting for the results of the pregnancy test, the efficacy of psychosocial interventions on anxiety, depression, and stress could not be established. Nevertheless, the self-administered Positive Reappraisal Coping intervention was found to be effective at enhancing the positive affect or dispositional optimism, which could make the waiting period more tolerable for infertile couples.

Limitations

There are limitations in this review. Unlike previous systematic reviews, this study adopted the methodology of descriptive analysis. However, the considerable heterogeneity among the interventions that were adopted, including the type, timing, number of sessions, duration, format, and delivery person, would inevitably affect the achievement of a reliable conclusion drawn from a meta-analysis. This might have contributed to the inconsistent or even contradictory conclusions derived from the four earlier reviews [17–20]. Second, grey literature, uncontrolled studies, and controlled studies relating to this topic were not included. Thus, it is possible that some promising interventions with a non-RCT design might have been neglected. Nevertheless, it was decided to only include RCT studies because the RCT is considered the best design to establish cause and effect [21]. There is also a limitation in that only papers written in English or Chinese were included due to language barriers. [47]

Conclusion

This review indicated that the effects of various interventions on the anxiety level, pregnancy rates, or marital function of infertile individuals/couples could not be confirmed due to methodological issues. None of studies reviewed showed

efficacy in improving the depression or stress levels of the individuals or couples undergoing IVF treatment. The mental health of the couples during the time that they were waiting for the result of their treatment was not tackled or measured in the included studies. Therefore, a new complex intervention, based on sound evidence, should be developed targeting both females and males of infertile couples undergoing IVF treatment, particularly during the stressful period of waiting before the result of the pregnancy test is revealed and after failed cycles. This program could focus on improving the mental health and marital function of the couples, which can probably be achieved by enhancing the partnership of the couples.

Compliance with ethical standard

Conflict of interest The authors declare that they have no conflict of interest.

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