human reproduction

ORIGINAL ARTICLE *Infertility*

Effectiveness of two guided self-administered interventions for psychological distress among women with infertility: a three-armed, randomized controlled trial

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STUDY QUESTION: What is the effect of two guided self-administered interventions on psychological distress in women undergoing IVF or ICSI?

SUMMARY ANSWER: A brief mindfulness intervention significantly reduced depression and improved sleep quality, while the gratitude journal intervention showed no significant effect on any outcome variables.

WHAT IS KNOWN ALREADY: Mindfulness and gratitude journal interventions have been found to be beneficial in reducing negative affect and improving well-being. However, there are very few mental health professionals who implement such interventions in low- and middle-income countries. Therefore, two guided self-administered interventions for women with infertility were designed to help them cope with their psychological distress.

STUDY DESIGN, SIZE, DURATION: A three-armed, randomized controlled trial was designed to evaluate the mindfulness and gratitude journal interventions for women undergoing IVF/ICSI. Between May 2016 and November 2017, at the reproductive center in a public hospital, 234 women were randomly assigned to the brief mindfulness group (BMG, $n = 78$), gratitude journal group (GJG, $n = 78$) or control group (CG, $n = 78$). The inclusion criteria were being a woman undergoing her first cycle of IVF, having at least junior middle school education and having no biological or adopted children.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Female infertility patients ($n = 346$) were approached, and 112 did not meet the inclusion criteria. All three randomized groups completed questionnaires on the day of down-regulation (T1), the day before embryo(s) transfer (T2), and 3 days before the pregnancy test (T3). The BMG completed four sessions and listened to a 20-minute audio daily, including guided mindfulness breathing and body scan. The GJG completed four sessions and wrote three gratitude journals daily. The CG received routine care. A generalized estimating equation was used in an intention-to-treat analysis. The primary outcome was depression. Secondary outcomes were anxiety, sleep quality, infertility-related stress, mindfulness and gratitude.

MAIN RESULTS AND THE ROLE OF CHANCE: Participants of the BMG showed decreased depression (mean difference (MD) = −1.69, [−3.01, −0.37], $d = 0.44$) and improved sleep quality (MD = −1.24, [−1.95, −0.39], $d = 0.43$) compared to the CG, but the effect was not significant for anxiety, Fertility Problem Inventory totals, mindfulness, gratitude scores or pregnancy rates. The BMG showed a significant

reduction in depression and improvement in sleep quality between T1 and T2, a continuous significant reduction between T1 and T3 and no reduction between T2 and T3. There were no significant effects on any of the variables for the GJG.

LIMITATIONS, REASONS FOR CAUTION: The inclusion criteria may result in bias because some participants with low education were excluded and only women with infertility were included. A low compliance rate occurred in the gratitude journals group. Moreover, men were not included in this study. Further research should consider including spouses of the target population.

WIDER IMPLICATIONS OF THE FINDINGS: The brief mindfulness intervention was beneficial in decreasing depression and improving sleep quality. Implementation of guided self-administered mindfulness could make the psychological counseling service more accessible for patients with infertility in resource-poor settings. The efficiency and feasibility of the gratitude journal intervention needs to be investigated further.

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Introduction

Infertility, as a major life adversity, can bring couples as much emotional strain as a traumatic event and may be particularly devastating for women (Verhaak *et al.*, 2007; Noorbala *et al.*, 2008). It is widely recognized that infertile patients undergoing IVF treatment experience high levels of psychological distress because of infertility itself, intrusive medical procedures, high costs and unpredictable outcomes (Verhaak *et al.*, 2007; Matthiesen *et al.*, 2012; Frederiksen *et al.*, 2015). The emotional status of infertile patients has been described as an 'emotional rollercoaster' during the IVF cycle (Matthiesen *et al.*, 2012). Patients' psychological distress showed significant correlations with poor marital quality (Wang *et al.*, 2007), unsuccessful IVF treatment (Domar *et al.*, 2011), isolation, social anomy (Noorbala *et al.*, 2008), domestic violence and divorce (Hajizade-Valokolaee *et al.*, 2017), and it interfered with many aspects of their lives. Unfortunately, there are few established treatments for infertility-related distress among women.

According to the ESHRE Guidelines and Guidelines for Counseling in Infertility (Boivin *et al.*, 2001; Gameiro *et al.*, 2015), infertility centers should provide psychosocial and emotional assistance for patients. Currently, there is an increasing trend in research on psychological interventions for these patients. Several reviews and meta-analyses regarding the efficacy of psychosocial interventions on outcome variables were inconclusive. Three systematic reviews (de Liz and Strauss, 2005; Ying *et al.*, 2016; Chu *et al.*, 2017) found that a nonpharmacological intervention had a significant effect in reducing negative emotions (Boivin, 2003; de Liz and Strauss, 2005; Frederiksen *et al.*, 2015) and improving pregnancy rates (Hammerli *et al.*, 2009; Frederiksen *et al.*, 2015), as well as marital function (Ying *et al.*, 2016). Other meta-analyses and reviews found no significant effect for psychological interventions in changing mental health (Hammerli *et al.*, 2009; Ying *et al.*, 2016; Chu *et al.*, 2017) or pregnancy rates (Boivin, 2003). Therefore, it is necessary and urgent to further investigate the effects of psychological interventions in infertility.

Mindfulness has been used increasingly and almost exponentially in various professional fields and disciplines (Wamsler *et al.*, 2018), ranging from medicine, psychology, military (Johnson *et al.*, 2014; Polusny *et al.*, 2015) and prisons (Samuelson *et al.*, 2007; Witkiewitz *et al.*, 2014) to the performing arts, pedagogy and business (Kabat-Zinn, 2003; Creswell, 2017; Wamsler *et al.*, 2018). Some encouraging studies indicate that mindfulness interventions reduce depressive and anxiety symptoms (Boettcher *et al.*, 2014; Strauss *et al.*, 2014; Hoge *et al.*, 2015; Eisendrath *et al.*, 2016), chronic pain (Garland *et al.*, 2014; Morone *et al.*, 2016), substance abuse (Brewer *et al.*, 2011; Witkiewitz *et al.*, 2014) and physical symptoms and improve quality of life (Gaylord *et al.*, 2011; Montgomery *et al.*, 2016). However, relatively few studies have examined mindfulness-based programs to alleviate the negative emotions of infertility patients. A study conducted with nine patients and no control group indicated that well-being and psychological distress of women with fertility were significantly improved after mindfulness-based cognitive therapy for 8 weeks (Sherratt and Lunn, 2013). Two non-randomized controlled studies revealed that women with infertility showed a significant decrease in depressive symptoms, shame and passive-avoidance coping strategies for the mindfulness-based intervention (MBI) group, while they also presented a statistically significant improvement in mindfulness skills, fertility, quality of life and self-efficacy compared with the control group (Galhardo *et al.*, 2013; Li *et al.*, 2016).

Mindfulness is described as an awareness characterized by paying intentional and nonjudgmental attention to the present moment (Kabat-Zinn, 1994). One standardized MBI featured weekly sessions of 2 to 2.5 h with a certified mindfulness therapist for 8 weeks, 45 minutes of daily home practice and a 1-day retreat of 6–8 h (Grossman, 2011, Compen *et al.*, 2018). However, professional therapists for mindfulness training are very scarce in low- and middle-income countries, and a classic MBI requires a significant time commitment and the availability of therapists. Therefore, a modified mindfulness intervention—brief and guided self-administered—is necessary to adapt programs to the shortage of mental health workers and infrastructure.

In addition, as a psychological intervention, gratitude has been conceptualized as an emotion, an attitude, a moral virtue, a habit, a personality trait or a coping response (Emmons and McCullough, 2003; Froh *et al.*, 2008) and is a wider life orientation toward focusing on and appreciating the positives in the world (Wood *et al.*, 2010;

O'Leary and Dockray, 2015). Gratitude journals have been the most frequently studied method in gratitude interventions because they are simple and easy to use (Wood et al., 2010). Gratitude practice was to guide people to think more about the positive aspects of a difficult situation and dwell less on its negative aspects (Froh et al., 2008; Lambert et al., 2012). A 'classic' gratitude intervention involves listing three good things for which a person is grateful for 3 weeks (Seligman et al., 2005). Specifically, participants may be asked to keep a dairy, in which they write three things, whether large or small, for which they are grateful and a causal explanation for each good thing, which is to be completed every day (Seligman et al., 2005; Froh et al., 2008; Wood et al., 2010; O'Carroll, 2017).

Although gratitude has not been as widely used in practice as mindfulness, gratitude and mindfulness interventions have similar effectiveness in that they may buffer against negative outcomes and increase well-being in diverse populations. A body of evidence indicated that gratitude interventions have been shown to reduce depression (Froh et al., 2008; Lambert et al., 2012), improve well-being (Wood et al., 2008) and decrease stress levels (Wood et al., 2010). Gratitude is distinct from mindfulness in definition and practice, but both share the essence of simplicity and accessibility (Wood et al., 2010; Creswell, 2017). Given that brief mindfulness-based and gratitude journal interventions are both tools for self-help, they minimally disrupt daily routines and are cost-effective (Cheng et al., 2015; Shao et al., 2016; Creswell, 2017). The present study was designed to assess the effect of both interventions (using two intervention groups and a control group) on negative emotions in a sample of patients undergoing infertility treatment.

The primary objective of the present study was to compare the effectiveness of both the brief mindfulness group (BMG) and the gratitude journal group (GJG) with a control group (CG) in terms of reducing psychological distress among women with infertility. We anticipated that the two interventions would be significantly more effective than the control condition. We expected the BMG and GJG to show a significant reduction in depression, anxiety, sleep quality and Fertility Problem Inventory (FPI) totals, along with significant increases in mindfulness, gratitude and pregnancy rate. Our hypothesis for both intervention groups was that depression levels at T2 and T3 would be significantly lower than at T1 (see below for details of T1, T2 and T3), and at T3 lower than at T2. In other words, there would be a gradual, significant downward trend in depression levels, whereas in the control group this would not be the case.

Materials and Methods

Trial design

The study was registered as a clinical trial (ChiCTR-IOR-16008452), and approval was obtained from the ethical review board of the Ningxia Medical University. This was a single-center, three-armed, randomized, controlled trial, following Consolidated Standards of Reporting Trials (CONSORT) guidelines, to assess the effects of brief mindfulness and gratitude journal interventions on primary and secondary outcomes.

Participants

Eligible women were recruited at the Reproductive Medicine Center in a hospital in Ningxia Province, China, between May 2016 and November 2017. The inclusion criteria were being a woman undergoing her first cycle of IVF, having at least junior middle school education, consenting to take part in the study and having no biological or adopted children. Exclusion criteria were not interested in the research, a diagnosed psychiatric disorder, prior experience in mindfulness and undergoing frozen embryo transfer.

Sociodemographic information and disease-related variables included age, ethnic group, education, marital status, occupation, family income, family type, duration of infertility, causes of infertility, type of treatment and number of abortions.

Procedures

A total of 346 women were approached on the day of down-regulation (the process of reducing or suppressing the body's response to specific stimuli: here, GnRH agonists or GnRH antagonists were used before IVF treatment to suppress the production of FSH and LH that trigger egg development and ovulation). Of the recruited participants, 112 were excluded because they did not meet the eligibility criteria. A trained nurse was responsible for recruitment and evaluation of participants.

The remaining 234 women provided written informed consent and were randomly assigned to the BMG ($n = 78$), GJG ($n = 78$) or CG ($n = 78$). Participants completed a 15-minute interview and the baseline self-report questionnaires on the day of down-regulation (T1: pre-intervention baseline) in a private room at the Reproductive Medicine Center. Information on demographics, clinical characteristics and outcome variables (depression, anxiety, sleep quality, FPI total, mindfulness and gratitude) were collected. Participants in the BMG and GJG received the intervention (the first session) immediately after T1 evaluation.

Assessment at T2 took place 1 day before embryo(s) transfer, and participants completed the T2 questionnaires (depression, anxiety, sleep quality, mindfulness and gratitude). The T3 follow-up assessment took place 3 days before the pregnancy test (Domar et al., 2015), and the same questionnaires were completed as at T1. The study protocol and assessment schedule are shown in Fig. 1.

Sample size

The sample size was estimated using power calculations with G∗Power 3 (Black et al., 2015). On the basis of mean treatment effects of a prior meta-analysis study ($d = 0.59$, or medium size) (Frederiksen et al., 2015), an estimated total sample size of 172 was required to detect a depression significant between-group effect for depression with 90% power and a two-sided $P < 0.05$. A 30% attrition rate was anticipated, making our total target recruitment 224.

Randomization and blinding

The random assignment sequence was obtained via a computerized random number generator. A statistician independent from the trial provided the randomization identification numbers to assign participants to each condition, using sequentially numbered, opaque, sealed envelopes, and that person did not interact with the participants. The trained nurse assessing the questionnaires at the three time points had
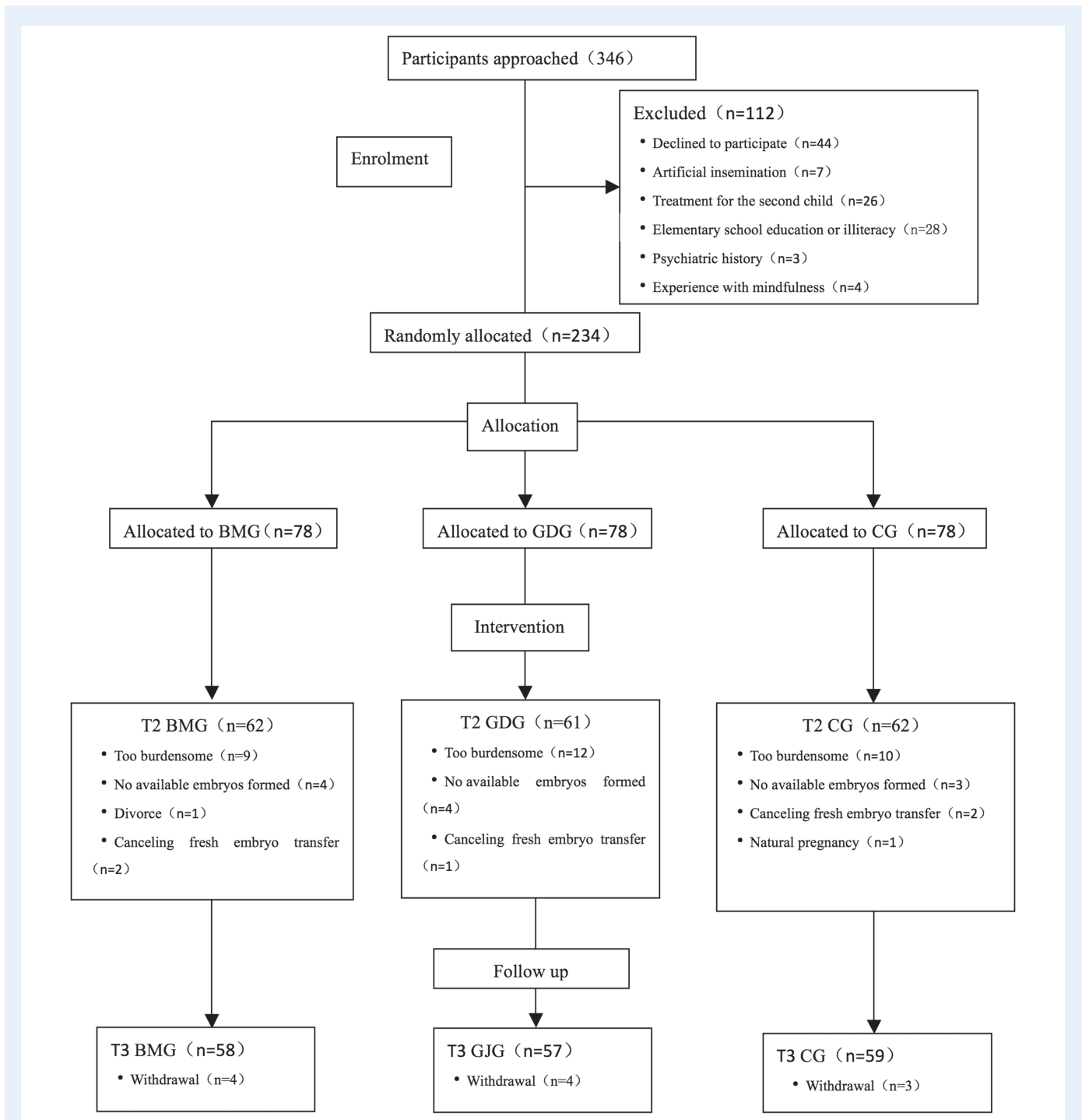
Participants approached（346）

Enrolment

Excluded（n=112）
- Declined to participate（n=44）
- Artificial insemination（n=7）
- Treatment for the second child（n=26）
- Elementary school education or illiteracy（n=28）
- Psychiatric history（n=3）
- Experience with mindfulness（n=4）

Randomly allocated（n=234）

Allocation

Allocated to BMG（n=78）　　Allocated to GDG（n=78）　　Allocated to CG（n=78）

Intervention

T2 BMG（n=62）
- Too burdensome（n=9）
- No available embryos formed（n=4）
- Divorce（n=1）
- Canceling fresh embryo transfer（n=2）

T2 GDG（n=61）
- Too burdensome（n=12）
- No available embryos formed（n=4）
- Canceling fresh embryo transfer（n=1）

T2 CG（n=62）
- Too burdensome（n=10）
- No available embryos formed（n=3）
- Canceling fresh embryo transfer（n=2）
- Natural pregnancy（n=1）

Follow up

T3 BMG（n=58）
- Withdrawal（n=4）

T3 GJG（n=57）
- Withdrawal（n=4）

T3 CG（n=59）
- Withdrawal（n=3）

Figure 1 **Study protocol and assessment schedule.** BMG, brief mindfulness group; GJG, gratitude journals group; CG, control group.

no access to the allocation sequence. Participants remained blind to the study hypotheses and the content of the other intervention method throughout the study.

Interventions

During the intervention phase, the BMG completed a weekly session of 1 h for 4 weeks and at least 20 minutes of daily practice at home (Rees *et al.*, 2018), led by the first author (C.F.B.), who has a nation-

ally approved psychology counselor certificate. After the intervention session began, participants were invited to listen to at least 20 minutes of audio-based practice daily, including guided mindfulness breathing and body scan. The four sessions occurred in a conference room at the Reproductive Medicine Center. The first session was delivered immediately after the baseline assessment on the day of down-regulation (T1), and the content involved the prevalence of infertility, information about the psychological distress of infertile women, an
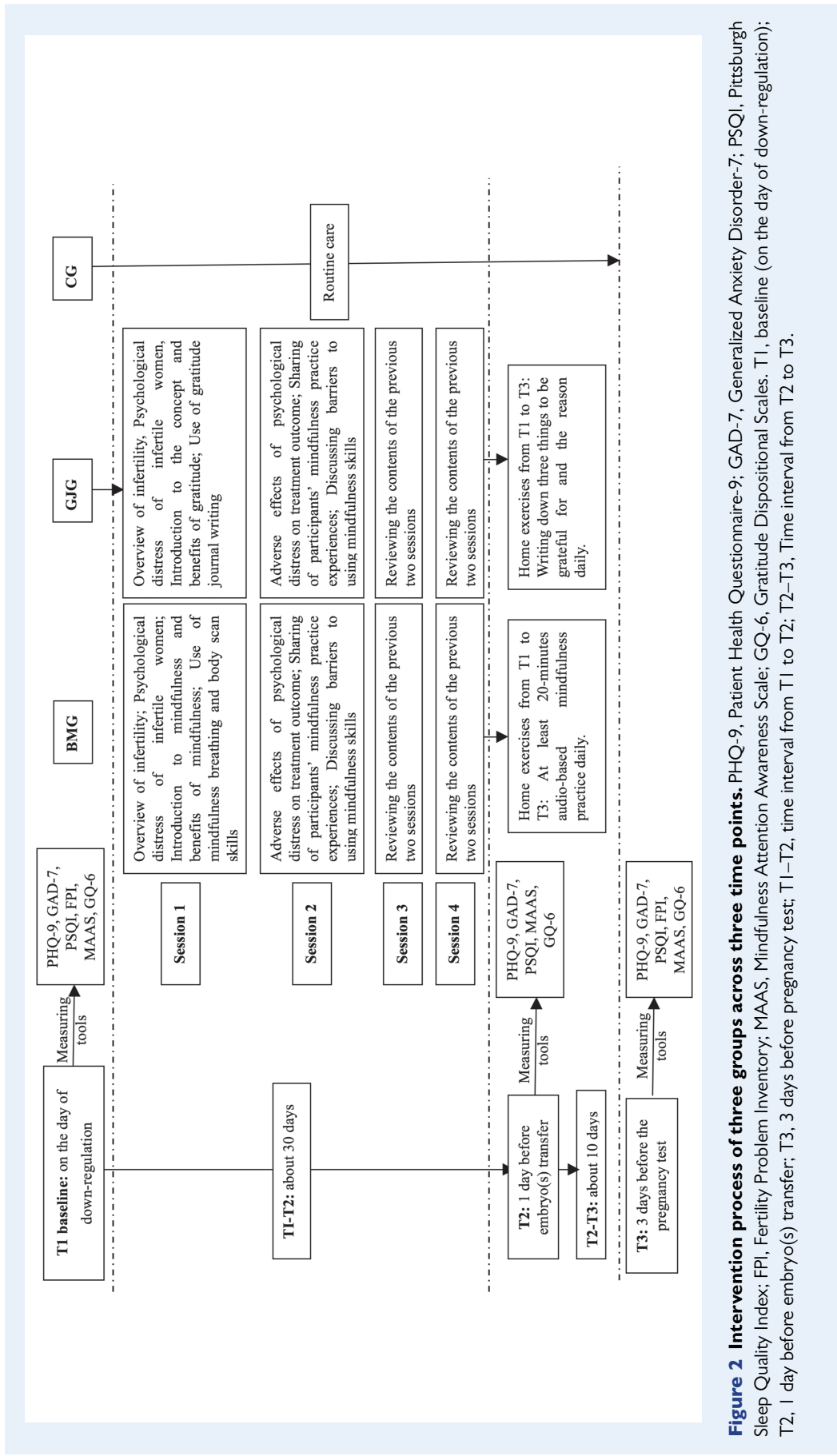
Figure 2 Intervention process of three groups across three time points. PHQ-9, Patient Health Questionnaire-9; GAD-7, Generalized Anxiety Disorder-7; PSQI, Pittsburgh Sleep Quality Index; FPI, Fertility Problem Inventory; MAAS, Mindfulness Attention Awareness Scale; GQ-6, Gratitude Dispositional Scales. T1, baseline (on the day of down-regulation); T2, 1 day before embryo(s) transfer; T3, 3 days before pregnancy test; T1–T2, time interval from T1 to T2; T2–T3, Time interval from T2 to T3.

introduction to mindfulness, benefits of mindfulness and mindfulness breathing and body scan skills. The second session covered the adverse effects of psychological distress on treatment outcome, sharing of participants' mindfulness practice experiences (Romcevich et al., 2018) and discussing barriers to using mindfulness skills on the day of the blood test ~2 weeks after down-regulation. The third session included reviewing the contents of the previous two sessions. The fourth session was the same as the third session and took place on the last day of the hormone therapy (see Fig. 2).

The GJG also completed a weekly session of 1 h for 4 weeks and the three gratitude journals exercise daily at home, led by the first author. Participants were instructed to write three things they were grateful for (even if these were small things) every day and the reason for their gratitude. The following instructions were provided: 'Thank someone or something, and mention why' (for example, 'Thanks to my husband, because he cooked for me today'; 'Thanks to my mother-in-law, because she supported me to seek the infertility treatment'). The four sessions involved knowledge of infertility, and the time points were the same as those for the BMG. The contents included an introduction to positive psychology, the concept of gratitude and the benefits and use of gratitude journal writing. Participants were instructed to write three gratitude journals every day (see Fig. 2).

The CG participants received routine care and were instructed to complete the questionnaires at each time point.

Each patient in the interventions was given two handouts. The first was an explanatory leaflet about the content of the four sessions, as described above, and the daily use of either mindfulness or gratitude skills. The second self-completed handout by participants records whether the participants completed the mindfulness practice and home mindfulness practice duration for the BMG, or the daily gratitude journal writing and the number of gratitude journals completed for GJG.

Measures

Primary outcome

Depression, the primary outcome, was measured using the Patient Health Questionnaire-9 (PHQ-9) scale, which contains nine items based on the diagnosis of *Diagnostic and Statistical Manual of Mental Disorders: Fourth Edition* depressive disorders. It is a reliable and valid measure with well-established psychometric properties (Feng et al., 2016), with each item scored as 0 (not at all), 1 (several days), 2 (more than half of the days) or 3 (nearly every day), and total scores for all items ranging between 0 and 27 (Kroenke et al., 2001). Each question asks patients to rate the frequency of the depressive symptoms that they experienced in the past 2 weeks (Wang et al., 2014). In this study, Cronbach's alpha was 0.860.

Secondary outcomes

Anxiety was assessed with the Generalized Anxiety Disorder-7 (GAD-7) scale, which has been proven to be a valid and efficient screening tool. It is a seven-item self-rating instrument (Spitzer et al., 2006). High internal consistency for the responses scale was found in the present study (Cronbach's alpha = 0.914).

Sleep quality was assessed by the Pittsburgh Sleep Quality Index (PSQI), a widely used and validated 19-item self-report questionnaire about sleep disturbances experienced over the past month (Black et al., 2015). Cronbach's alpha was 0.754 in the present study.

We used the Chinese language version of the FPI, a reliable instrument with good discriminative value, to measure infertility-related stress (Cronbach's alpha = 0.840) (Peng et al., 2011).

The Mindfulness Attention Awareness Scale (MAAS) was shown to be a reliable and valid instrument to measure respondents' mindfulness disposition (Brown and Ryan, 2003), and Cronbach's alpha was 0.850.

The Gratitude Dispositional Scales (GQ-6) assess an individual's disposition to express gratitude, and it consists of six items scored on a seven-point Likert scale (Kong et al., 2017). Cronbach's alpha was 0.803.

Finally, the biochemical pregnancy rate was assessed via a blood test to measure hCG performed 2 weeks after embryo transfer.

Treatment fidelity

The intervention groups recorded how long they spent listening to the mindfulness audio recording or writing the gratitude journal each day. WeChat is a popular instant messaging software package in China, and the participants in the two intervention groups received a reminder by WeChat at 3-day intervals, including reminders about the intervention exercises and information about infertility included in routine care in IVF cycles. Thus, there were eight reminders in total. Each exercise reminder invited participants to continue their daily practice of mindfulness or gratitude journal writing, respectively (Cavanagh et al., 2013). The control group received eight messages that included only the information about infertility. All three groups received identical information about infertility to eliminate non-specific treatment influences on the outcomes.

Treatment credibility

Feasibility was assessed by the rate of completion, using the records kept by the participants. The completion rate is a ratio of actual home-based practice days divided by total intervention days and expressed as a percentage. We evaluated completion rate of home practice as a reference of two-thirds of the assigned amount (67%) (Parsons et al., 2017).

Statistical analyses

Statistical analyses used the Statistical Package for the Social Sciences, version 20 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean and SD, while categorical variables were expressed as percentages. The chi-square (χ^2) test and one-way ANOVA were used to compare baseline values between the intervention and control groups. We conducted generalized estimating equations (GEEs) analyses (de Bruin et al., 2016) to examine whether the interventions differed in terms of effects on the dependent variables compared with the control group. Missing data were handled using the last-observation-carried-forward method. The results were adjusted for age, marital status, education level, duration of infertility and causes for infertility, based on the literature (Drosdzol and Skrzypulec, 2009; Ogawa et al., 2011; Alhassan et al., 2014; Al-Asadi and Hussein, 2015; Koochaksaraei et al., 2016). The effect of the interventions was analyzed by comparing the differences between the intervention and control groups according to the 'intention-to-treat' (ITT) principle, and a per-protocol analysis on complete data was undertaken as a sensitivity analysis. Because of the multiplicity of secondary endpoints, results were evaluated using a two-tailed test

(statistical significance set at $P < 0.01$). Cohen's d measured effect sizes, and these were interpreted as small (0.2 to 0.5), medium (0.5 to 0.8) or large (0.8).

Results

Treatment acceptability

Acceptability was the degree to which the intervention was accepted by a patient. After the T3 assessment, we found that the compliance rate of gratitude intervention was very low. Participants were questioned about the incomplete gratitude journals, and they also gave some reasons for this. The information was displayed below, which was reported by patients and was not based on measurements. Specifically, the information was obtained from the participants' actual experience in IVF cycles, rather than a well-designed method.

For mindfulness, only one woman reported that she was bored listening to the mindfulness audio. Two women reported it was easy to sleep during the audio.

For the gratitude journal, two women stated that it was hard for them because it seemed like a homework assignment from a teacher. Seven women reported that their husband or mother-in-law did not think writing a gratitude journal was beneficial for pregnancy, and one husband threw away his wife's journal during the embryo transfer period. Five women reported that after they maintained the gratitude journal for several days, they could not find new things to write, so they repeated what they had written before, as they did the same things every day. Six women reported there was nothing to be grateful for: two of them suffered chronic physical and verbal violence, while the other four were in unhappy marriages and had lived for a long time with their in-laws.

Study flow

There were no significant differences in baseline demographics, clinical characteristics or psychological variables between the intervention and control groups (Table I). Fig. 1 shows the study flow chart and reasons for ineligibility. Of 346 patients approached by the researcher, 44 declined participation, 7 were excluded because of artificial insemination, 26 were pursuing treatment for a second child, 28 had low educational attainment, 3 reported a mental illness and 4 had previous experiences with mindfulness. In total, 234 patients were randomly assigned to BMG, GJG and CG.

The mean session attendance did not differ between the BMG (2.75 ± 0.90) and GJG (2.71 ± 0.78). For the BMG, in the T1–T2 stage, the mean ($\pm$SD) number of days of intervention was 30.79 ± 1.64, and the mean number of days of actual home practice was 20.82 ± 6.09. Thirty-six patients completed at least 67% of home practice. In the T2–T3 stage, the total number of days was 10, and the mean number of days of actual home practice was 8.61 ± 2.33, with 42 patients completing at least 67% of their home practice.

For the GJG, in T1–T2 stage, the mean number of days of intervention was 31.53 ± 2.28, and the mean number of days of actual home practice was 14.61 ± 6.09. Six patients completed at least 67% of home practice. In the T2–T3 stage, the total number of days was 10, and the mean number of days of actual home practice was 4.11 ± 1.83, with only two patients completing at least 67% of home practice.

No adverse events occurred during the study.

Depression

First, we performed an overall global test in ITT principle. The GEE-adjusted models for the effect of the interventions on outcome variables showed a significant group-by-time interaction (Wald $\chi^2 = 13.87$, $P = 0.008$), a significant main effect of time (Wald $\chi^2 = 22.42$, $P < 0.001$) but no significant main effect of group (Wald $\chi^2 = 3.42$, $P = 0.181$) for depression (Table II).

Fig. 3a' shows that a significant difference was observed between BMG and CG at T2 (MD $= -1.69$, $[-3.01, -0.37]$, $d = 0.44$) and T3 (MD $= -1.84$, $[-3.11, -0.58]$, $d = 0.31$) for depression, while the comparison of GJG to CG showed no difference at either T2 (MD $= -0.91$, $[-2.24, 0.23]$, $d = 0.30$) or T3 (MD $= -0.39$, $[-1.77, 0.98]$, $d = 0.11$). Fig. 3a summarizes the trends in depression scores across the three groups. For the BMG, depression decreased significantly from T1 to T3, which included a significant reduction from T1 to T2, while there was no significant reduction from T2 to T3.

The control group reported no significant changes between the three time points (Table III and Fig. 3a). The results of the sensitivity analysis of a per-protocol analysis are presented in Supplementary Table SI.

Anxiety

The results for anxiety in GEE-adjusted models indicated no significant effect of time (Wald $\chi^2 = 8.22$, $P = 0.016$) and no significant main effect of group (Wald $\chi^2 = 0.47$, $P = 0.790$) or group-by-time interaction (Wald $\chi^2 = 8.39$, $P = 0.078$) (Table II). Fig. 3b shows that the anxiety level in the BMG decreased significantly from T1 to T2 ($P < 0.001$, $d = 0.31$) and from T1 to T3 ($P < 0.001$, $d = 0.24$), while neither the GJG nor the CG showed significant changes across the three time points. However, Table II and Fig. 3b' showed no substantial differences between BMG and CG, GJG and CG at T2 and T3.

Sleep quality

GEE-adjusted models resulted in a significant main effect of time (Wald $\chi^2 = 16.60$, $P < 0.001$), a significant group-by-time interaction (Wald $\chi^2 = 14.07$, $P = 0.005$) and a nonsignificant group main effect (Wald $\chi^2 = 4.55$, $P = 0.103$) for the PSQI (Table II). Figure 3c' shows that there was a significant difference at T2 (MD $= -1.24$, $[-1.95, -0.39]$, $d = 0.43$) and no difference at T3 (MD $= -0.89$, $[-1.90, 0.14]$, $d = 0.30$) for sleep when BMG and CG were compared. GJG and CG were not substantially different (Table II and Fig. 3). Fig. 3c shows that the PSQI score decreased significantly from T1 to T2 ($P < 0.001$, $d = 0.57$) and from T1 to T3 ($P = 0.001$, $d = 0.42$) for BMG. In contrast, the GJG and CG reported no significant changes between the time points (Table III and Fig. 3c).

Other outcome variables

Table II shows that, for the three groups, the main effects of group and time on FPI total, MAAS and gratitude scores were not significant, and the group-by-time interaction also was not significant. Moreover, mean differences on FPI total, MAAS and gratitude were not significant between the two intervention groups and the control group (Fig. 3). As for pregnancy rate, there was no significant difference between

Table I Baseline sociodemographic data, clinical characteristics, and outcome variables of the three groups (n = 234).

Variables		BMG (n = 78)	GJG (n = 78)	CG (n = 78)
Age, mean (SD), years		30.23 (4.14)	30.27 (4.14)	30.36 (4.82)
Ethnicity	Han	58	54	62
	Hui	20	24	16
Marital status	First marriage	71	72	69
	Remarriage	7	6	9
Education	junior or senior	56	50	56
	college or above	22	28	22
Location	Rural	10	13	11
	Suburban	10	14	15
	Urban	58	51	52
Occupation	Unemployed	14	14	16
	Employee	64	64	62
Family income (Yuan/monthly)	≤3000 Yuan	22	23	20
	>3000 Yuan	56	55	58
Family type	Only live with your spouse (ref.)	61	58	61
	Others	17	20	17
Duration of infertility, mean (SD), years		3.96 (2.77)	4.29 (3.05)	3.66 (3.08)
Type of treatment	IVF	52	60	54
	ICSI	25	18	24
Causes for infertility	Male	15	11	18
	Female	30	32	32
	Both	19	14	13
	Unexplained	14	21	15
Number of abortions, mean (SD)		0.56 (1.03)	0.35 (0.70)	0.50 (0.80)
Depression (PHQ-9), mean (SD)		7.87 (5.15)	7.78 (5.61)	7.90 (4.31)
Anxiety (GAD-7), mean (SD)		6.56 (4.44)	6.35 (5.14)	5.91 (3.92)
Sleep (PSQI), mean (SD)		7.73 (2.95)	7.63 (2.68)	7.46 (3.09)
FPI total, mean (SD)		156.79 (30.44)	159.33 (28.54)	159.31 (25.97)
MAAS, mean (SD)		55.31 (10.06)	55.53 (11.11)	56.54 (10.82)
GQ-6, mean (SD)		31.23 (5.80)	30.62 (5.83)	31.06 (5.65)

m, mean; BMG, brief mindfulness group; GJG, gratitude journals group; CG, control group; PHQ-9, Patient Health Questionnaire-9; GAD-7, Generalized Anxiety Disorder-7; PSQI, Pittsburgh Sleep Quality Index; FPI, Fertility Problem Inventory; MAAS, Mindfulness Attention Awareness Scale; GQ-6, Gratitude Dispositional Scales.

the three groups (BMG: 38/58, GJG: 26/57, CG: 30/59; $\chi^2 = 4.95$, $P = 0.084$).

Per-protocol analytical approaches

We also performed per-protocol analytical approaches on the data, and the results were no different between ITT and per-protocol analysis. The results of per protocol analysis are shown in the Supplementary Table SII.

Discussion

The findings of this study partly support the research hypothesis. The brief mindfulness intervention was shown to have a beneficial effect in decreasing depression and improving sleep quality compared to the control condition, although this approach did not significantly affect anxiety, FPI total, mindfulness, gratitude scores or pregnancy rate. The gratitude journal intervention had no significant effect on any variables, compared with the control group. The partial support occurs only in the first phase of the study, between time points T1 and T2, and only for the BMG. No variables showed any significant difference across the three time points for the gratitude journal intervention.

Our main results indicated that a brief mindfulness intervention made a significant contribution to the decrease of depression, which was consistent with the study conducted by Galhardo *et al.* (2013). Mindfulness skills aim to foster the capacity to adopt an attitude of openness or acceptance with a curious, detached and nonreactive orientation that replaces our default and mindless thinking (Creswell,

Table II Results of the overall global test and mean difference between-groups for the outcome measures in the generalized estimating equations analysis in intention-to-treat principle.

Variable		MD $_{BMG-CG}$ (n = 78)	MD $_{GJG-CG}$ (n = 78)	Group effect		Time effect		Group × time effect	
				Wald χ^2	P	Wald χ^2	P	Wald χ^2	P
Depression (PHQ-9)	T1	−0.03 (−1.53, 1.60)	−0.12 (−1.62, 1.34)	3.42	0.181	22.42	**<0.001**	13.87	**0.008**
	T2	**−1.69 (−3.01, −0.37)** *	−0.91 (−2.24, 0.23)						
	T3	**−1.84 (−3.11, −0.58)** **	−0.39 (−1.77, 0.98)						
Anxiety (GAD-7)	T1	0.65 (−0.59, 2.05)	0.44 (−0.86, 1.99)	0.47	0.790	8.22	0.016	8.39	0.078
	T2	−0.48 (−1.76, 0.80)	0.05 (−1.30, 1.41)						
	T3	−0.54 (−1.86, 0.70)	−0.16 (−1.21, 1.56)						
Sleep (PSQI)	T1	0.27 (−0.63, 1.25)	0.17 (−0.71, 1.09)	4.55	0.103	16.60	**<0.001**	14.07	**0.005**
	T2	**−1.24 (−1.95, −0.39)** **	−0.12 (−1.08, 0.81)						
	T3	−0.89 (−1.90, 0.14)	−0.16 (−1.19, 0.88)						
FPI total	T1	−2.52 (−10.58, 7.96)	0.02 (−8.25, 8.36)	0.22	0.897	3.30	0.070	0.36	0.834
	T2								
	T3	−2.91 (−13.73, 7.92)	−0.61 (−10.46, 9.24)						
Mindfulness (MAAS)	T1	−1.23 (−4.49, 2.02)	−1.13 (−4.25, 2.42)	1.18	0.555	2.70	0.26	5.49	0.241
	T2	2.62 (−0.92, 6.88)	0.12 (−3.82, 3.92)						
	T3	0.56 (−2.71, 4.33)	0.32 (−4.83, 4.09)						
Gratitude (GQ-6)	T1	0.17 (−1.57, 1.72)	−0.44 (−1.53, 0.81)	2.32	0.314	5.37	0.068	2.33	0.675
	T2	−0.39 (−1.04, 1.53)	−1.16 (−2.58, 0.45)						
	T3	0.12 (−1.43, 1.63)	−0.93 (−2.79, 1.06)						

*$P < 0.01$, ** $P < 0.001$. Generalized estimating equations adjusted models show mean difference and 95% CI between groups for the outcome measures. The values in bold are the ones that are statistically significant.

MD, mean difference; T1, baseline (on the day of down-regulation); T2, 1 day before embryo(s) transfer; T3, 3 days before pregnancy test. Generalized estimating equations models adjusted some potential confounding factors: age, marital status, education level, duration of infertility and causes for infertility.

2017). Depressive symptoms are related to negative affect or distorted thoughts (Galhardo et al., 2013). This process of turning attention and awareness toward the present moment experience, including internal and external events, thoughts and emotions, was assumed to help members of the BMG to disengage from negative feelings of worthlessness and self-reproach caused by infertility and may expectedly result in women with infertility being less focused on and entangled with their infertility problem and adopting a less self-critical attitude (Galhardo et al., 2013; Creswell, 2017). This may explain why mindfulness contributed to the reduction in depression among women with infertility. Furthermore, the higher completion rate in this study was consistent with that in another study, suggesting that a brief mindfulness exercise is more easily implemented in harder-to-reach populations (Creswell, 2017). Therefore, this low-cost self-help approach may be an applicable intervention for infertile women in resource-poor settings.

Another promising result was that the BMG showed improved sleep quality. A study in 2008 showed that 34% of infertile women had sleep disturbances, and women with diminished ovarian reserves were nearly three times more likely to report sleep disturbances than those with other causes of infertility (Pal et al., 2008). Another study indicated that sleep disturbances affected more than one-third (35%) of infertile women during IUI treatment (Lin et al., 2014). A theoretical review of sleep disturbance in relation to infertility revealed that sleep dysregulation may affect infertility via three pathways (Kloss et al., 2015). First, insomnia may be associated with hypothalamic pituitary adrenal

activation, which leads to infertility. Second, sleep dysregulation may independently change a successful pregnancy by inhibiting or enhancing reproductive hormones. Third, sleep loss may also affect pregnancy through the immune system. Given this research and our findings, instructing infertile women to practice mindfulness every day may improve sleep quality, thereby possibly improving infertility treatment outcomes.

Our study revealed that the BMG treatment had no significant effect on pregnancy rates, consistent with another study (Domar et al., 2011). However, our results contradict the findings from another study that showed a statistically significant difference in MBI on pregnancy rates (Li et al., 2016). This apparent contradiction may stem from differences in the period of time studied and the extent of mindfulness practice. Further, pregnancy rate was defined as a biochemical pregnancy 2 weeks after embryo(s) transfer in our study, while the other study relied on clinical determinations or ultrasound readings tested 6 months after the intervention.

In other respects, the findings of our study are inconsistent with many studies that found that gratitude journaling boosted happiness or well-being and decreased negative emotions (i.e. depressive symptoms and stress) (Seligman et al., 2005; Cheng et al., 2015; Matvienko-Sikar and Dockray, 2017; O'Carroll, 2017). We speculated that one reason for the inconsistent results may be poor compliance of the GJG in our study. Even though the two intervention groups had similar content structures and implementation procedures and the mean session atten-
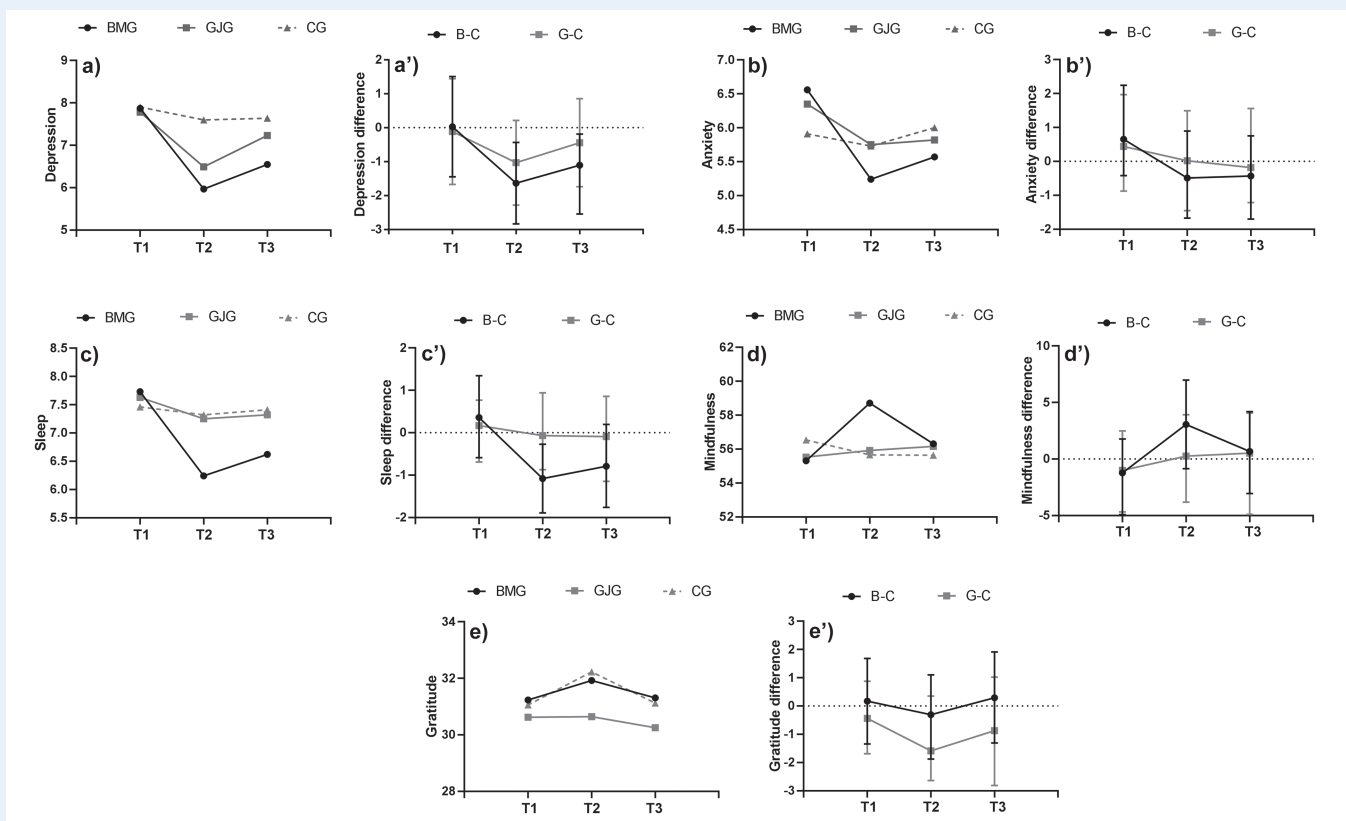
Figure 3 Means and mean difference for intervention groups and control group across the three assessment times. (**a**) Means for each group on depression across the three assessment times. (**a'**) Depression difference for two intervention groups with control group across the three assessment times. (**b**) Means for each group on anxiety across the three assessment times. (**b'**) Anxiety difference for two intervention groups with control group across the three assessment times. (**c**) Means for each group on sleep across the three assessment times. (**c'**) Sleep difference for two intervention groups with control group across the three assessment times. (**d**) Means for each group on mindfulness across the three assessment times. (**d'**) Mindfulness difference for two intervention groups with control group across the three assessment times. (**e**) Means for each group on gratitude across the three assessment times. (**e'**) Gratitude difference for two intervention groups with control group across the three assessment times. BMG, brief mindfulness group; GJG, gratitude journals group; CG, control group; T1, pre-test; T2, post-test; T3, follow-up; B-C, mean differences between BMG and CG; G-C, mean differences between GJG and CG. Adjusted mean with 95% CI.

dance did not differ meaningfully, compliance with home-based practice completion showed an enormous difference. It may not be that the intervention itself was ineffective but rather that the acceptability of the intervention on the part of the participants constituted an independent influence. While numerous studies provided evidence that gratitude journals are easy to implement in clinical settings because of the simple nature of the technique (Wood *et al.*, 2010), we did not expect that this approach may be difficult to use with infertile women in our region. We propose several reasons to explain the poor compliance with the gratitude intervention.

Gratitude is considered to be a promising clinical intervention. Gratitude not only arises from the aid of others but also is a capacity to focus on and appreciate positive aspects of life (Wood *et al.*, 2010). Gratitude practice can help individuals to develop positive emotions (Ramirez *et al.*, 2014). Therefore, for individuals with a low level of education it may be hard to immediately understand and act in a grateful way, despite the four sessions provided. A total of 69.2% of our study population had junior or senior school education, and some reported not knowing what to write after a few days, because

their lives consisted of repetitions of the same daily interactions with others, routines and tasks. Moreover, some indicated that writing three journals daily could add to their anxieties and stresses, rather than reduce them. To date, our results have not been reported in other studies, as the majority of participants in existing research had an educational level of bachelor's degree or above (Seligman *et al.*, 2005; Cheng *et al.*, 2015; O'Leary and Dockray, 2015; Matvienko-Sikar and Dockray, 2017; O'Carroll, 2017; Dunaev *et al.*, 2018).

In addition, the feasibility of gratitude techniques has been challenged. Gratitude includes both a trait and a state. The disposition toward gratitude must be based on experiencing positive emotions after a positive outcome and on subjective well-being (McCullough *et al.*, 2002; Emmons and McCullough, 2003). It may be blocked in negative environments and situations (Wood *et al.*, 2010). This explains why some participants who had experienced domestic violence and unhappy marriages reported having no one or nothing to be grateful for. This study raises the possibility, posed by Seligman, that individuals from other backgrounds and experiences may expose limits to the generality of positive interventions (Seligman *et al.*, 2005). Besides,

Table III **Mean scores and effect size between-groups and within-groups for outcome measures.**

Variable		BMG (n = 78)		GJG (n = 78)		CG (n = 78)		d BMG-CG	d GJG-CG
			d		d		d		
Depression (PHQ-9)	T1	7.87 (5.15)	Reference	7.78 (5.61)	Reference	7.90 (4.31)	Reference		
	T2	5.97 (3.93)	**0.41****	6.49 (3.92)	0.27	7.60 (3.51)	0.08	**0.44***	0.30
	T3	6.55 (3.64)	**0.30****	7.23 (4.20)	0.11	7.64 (3.37)	0.07	**0.31***	0.11
Anxiety (GAD-7)	T1	6.56 (4.44)	Reference	6.35 (5.14)	Reference	5.91 (3.92)	Reference		
	T2	5.24 (3.99)	**0.31****	5.75 (4.68)	0.12	5.73 (3.23)	0.05	0.13	0.00
	T3	5.57 (3.68)	**0.24****	5.82 (4.17)	0.11	6.00 (3.29)	0.02	0.12	0.05
Sleep (PSQI)	T1	7.73 (2.95)	Reference	7.63 (2.68)	Reference	7.46 (3.09)	Reference		
	T2	6.24 (2.28)	**0.57****	7.25 (2.60)	0.14	7.32 (2.74)	0.05	**0.43***	0.03
	T3	6.62 (2.25)	**0.42****	7.32 (2.80)	0.11	7.41 (2.98)	0.02	0.30	0.03
FPI total	T1	156.79 (30.44)	Reference	159.33 (28.54)	Reference	159.31 (25.97)	Reference		
	T2								
	T3	152.05 (34.32)	0.15	155.61 (29.40)	0.13	156.54 (24.56)	0.11	0.22	0.03
Mindfulness (MAAS)	T1	55.31 (10.06)	Reference	55.53 (11.11)	Reference	56.54 (10.82)	Reference		
	T2	58.71 (11.34)	**0.32***	55.92 (12.16)	0.03	55.66 (11.70)	0.08	0.26	0.02
	T3	56.31 (10.30)	0.10	56.16 (13.19)	0.05	55.64 (12.22)	0.08	0.06	0.04
Gratitude (GQ-6)	T1	31.23 (5.80)	Reference	30.62 (5.83)	Reference	31.06 (5.65)	Reference		
	T2	31.92 (6.38)	0.11	30.64 (5.90)	0.00	32.23 (6.28)	0.20	0.05	0.26
	T3	31.31 (6.22)	0.01	30.25 (7.17)	0.06	31.12 (6.18)	0.01	0.03	0.13

$*P < 0.01$, $**P < 0.001$. Generalized estimating equations adjusted models show mean difference between groups and within groups for outcome measures. The values in bold are the ones that are statistically significant.
d (Cohen's d): Effect size, change from baseline T1 to T3.
d_{BMG-CG}: Effect size of difference between the mindfulness group and control group.
d_{GJG-CG}: Effect size of difference between the gratitude group and control group.

disease factors should be considered when employing this method of intervention, as most patients were asked by their husband to lie down or rest in order to get pregnant after the embryo transfer. Their husband believed that writing a gratitude journal may add extra pressure on patients and be detrimental to pregnancy. Therefore, more research is needed to explore the feasibility of the gratitude intervention approach, with the aim to improve interventions targeted at patients with a lower education level and specific disease characteristics.

Our study affirmed previous findings regarding the effectiveness of mindfulness interventions for patients with infertility. Although standardized mindfulness interventions have been considered beneficial in many fields, the present research demonstrated that a brief mindfulness intervention (simple, low cost and self-administered with non-specialist therapists) was also effective and appropriate for populations in low- or middle-income countries. However, the gratitude journal intervention did not have an effect on any of the dependent variables, partly because of poor compliance. Furthermore, we also obtained valuable information concerning the reasons for poor compliance from patients that will help with improvements in future intervention programs.

Our research has several limitations. First, our inclusion criteria meant that low-education or illiterate patients were excluded from the study. Their exclusion may limit the generalizability of our findings. Future studies should include them. Second, the results may differ for those who experience more than one IVF cycle; thus, additional studies may determine the effects for women who have experienced more than one cycle. Third, another limitation was the exclusion of men, as research indicated that emotions of wives may interact with those of their husbands (Kim et al., 2018). In future studies, it is thus essential that the interventions also involve spouses. Fourth, the compliance rate was quite low for the gratitude journal group in our study, and the reason may be the participants' low levels of education, their living conditions and disease factors. Finally, this study was conducted in a single health center; therefore, the external validity of our findings may be limited; a multi-center study is needed.

To the best of our knowledge, this was the first study in which two guided self-administered and cost-effective interventions were used with infertile women in an economically poor area where mental health resources are in short supply. The sample size was large, and the study had a robust methodology. Our results suggest that the brief mindfulness intervention may be useful for clinical practice. However, the study needs replication to confirm the effects of the interventions and explore how they vary among differing groups of participants.

Conclusion

Taken together, our findings indicated that the brief mindfulness intervention decreased depression and improved sleep quality, suggesting its suitability for IVF patients. The approach is inexpensive, portable

and easy to use in a daily routine. Even so, more research is needed to examine the stability of the effect. Gratitude journaling had no significant effect on any outcome variables. Our study was intended to inform whether these two interventions were effective in reducing the negative emotions of infertile women, but it did not address questions about which type of intervention was best suited at the individual level. Future studies should develop alternative designs to examine this question. Furthermore, mental health planning and policies should facilitate the implementation of psychological services that are integrated into IVF treatment, to help women with infertility cope with psychological distress (Saxena et al., 2007).

Supplementary data

Supplementary data are available at *Human Reproduction* online.

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Authors' roles

All authors contributed to this study. F.-L.C. designed the trial and reviewed the manuscript. C.-F.B. designed the interventions and data collection tools and drafted and revised the paper. X.X., G.M. and Y.-Z.J. assisted with the recruitment of patients. N.-X.C., J.-W.S. and D.S. cleaned and analyzed the data. J.L., Q.-Q.Y. and X.Z. revised the paper.

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Conflict of interest

None declared.

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