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Research article

Preliminary examination of acceptability, feasibility, and effectiveness of internet-based cognitive behavioral therapy for treatment of depression and anxiety in infertile women

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A B S T R A C T

Background: Despite a large body of evidence supporting the effectiveness of internet-based cognitive behavior therapy (ICBT) for the treatment of depression and anxiety, there is no report of the efficacy of ICBT program in the Iranian population. The present study aimed to test the acceptability, feasibility, and effectiveness of ICBT program for the treatment of depression or anxiety in infertile women.

Method: This study consisted of two phases. In the first phase, we designed "Peaceful Mind", an eight-session therapist-guided ICBT program. In the second phase, we tested the efficacy of the program by conducting 2-arm parallel group, non-inferiority randomized control trial, between October 2020 and July 2021.60 infertile women diagnosed with depression or anxiety disorders were divided randomly to ICBT treatment (n = 30) and face-to face CBT (n = 30). The participants received individual CBT sessions (60 min, over 8 weeks) and completed the questionnaires at the beginning, in mid-trial, and 8 weeks after the trial. The outcomes comprised Beck Depression Inventory (BDI-II), Beck Anxiety Inventory (BAI, Fertility problem inventory (FPI), Client Satisfaction Questionnaire (CSQ-8), and System usability scale (SUS).

Results: The usability scores of the "Peaceful Mind" ICBT (M = 67.07, SD = 17.23, range = 1–100) and satisfaction with the treatment (M = 25.06, SD = 4.18, range = 1–32) were high. Patient adherence to the treatment in the ICBT group (86.6%) was the same as that in the CBT (73.3%). The between-group mean differences at the post-trial were −4.79 (CI 95% = −10.81 to 1.23) for depression scores and −4.15 (CI 95% = −9.52 to 1.22) for anxiety scores; both differences were within the non-inferiority margin points for the lower 95%CI.

Conclusion: "Peaceful mind" ICBT was found to be feasible and accessible for delivering the treatment to the patients. The study confirmed that both ICBT face-to face CBT were equally effective in reducing depression and anxiety of the patients.

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1. Introduction

Infertility is a prevalent condition in women in the reproductive age, which is often followed by psychological problems [1]. The prevalence of infertility is estimated to range between 8% and 12% worldwide [2,3]. Infertility has great psychological consequences on women [1,4]. The prevalence of psychological problems ranges from 48% to 96% in infertile women [5]. Individuals with infertility problem may suffer from stigma, social isolation, helplessness, shame, jealousy, loss of self-esteem, and loneliness [6–8]. Depression and anxiety are the most common mental problems associated with infertility [9]. Two recent meta-analyses reported the prevalence of 36% for anxiety and 50% for depression in infertile women [10,11]. Evidence supports the fact that depression and anxiety negatively affect ART process and reproductive outcomes [6,12,13].

It has been over two decades that Cognitive Behavioral Therapy (CBT) has been widely introduced for the treatment of anxiety and depression related to infertility [14–17]. Although evidence has confirmed the effectiveness of CBT on the improvement of psychological problems of infertile women, there is limited access to CBT therapists [16,18–20]. Internet-based CBT (ICBT) is an alternative self-help treatment that increases access to CBT and psychological care [21,22]. The advantages of ICBT include access to service, avoidance of stigma associated with seeing a therapist [23], more privacy and convenience [24], greater treatment fidelity, cost effectiveness [25], no geographic restrictions [26], and anonymity [27]. A recent meta-analysis confirmed the acceptability and effectiveness of ICBT for the treatment of depression and anxiety [28]. Evidence has supported that ICBT has the same effect as face-to-face CBT on the treatment of depression [29,30]. Other studies have reported that internet-based interventions with a therapist support are more efficient than those without a therapist support [31,32].

Whilst there is enough evidence regarding the effect of ICBT in the treatment of depression or anxiety [28], there is scarce information about internet-based psychotherapy in infertile women. Sexton et al. (2009) developed a Web-based Coping with Infertility to reduce stress in 31 infertile women. The results revealed that stress reduced in the Web-based group compared with that in the wait-list control group [33]. Schick et al. in a protocol study explained that they will develop a smart-phone-supported approach and test it in an RCT of two groups of women and men undergoing infertility treatment [34].

To improve access to evidence-based infertility care, we developed the ICBT program of 'Peaceful Mind' for the treatment of depression/anxiety of infertile women. To the best of our knowledge, the current study is the first to report the development of ICBT and compare the effectiveness of ICT with that of CBT on the treatment of depression/anxiety in women with infertility. Moreover, there are currently no national, regional, or local evidenced-based ICBT in use in Iran. This is the first report of the development of ICBT in Iran. The objectives of the study included: 1) testing the acceptable and feasible approach of ICBT for women with infertility, 2) evaluating the effectiveness of ICBT on the improvement of depression, anxiety, and infertility-associated stress in infertile women, 3) comparing the efficacy of ICBT to that of face-to-face CBT in the improvement of depression, anxiety, and infertility-associated stress in infertile women, and 4) comparing patient satisfaction and adherence in ICBT to those in face-to-face CBT.

2. Materials and methods

The study consisted of two phases. In the first phase, we designed "Peaceful Mind", an eight-session therapist-assisted ICBT program, for the treatment of anxiety and depression. In the second phase, we tested the efficacy of "Peaceful Mind" program by conducting a randomized control trial.

2.1. First phase: program development

"Peaceful Mind" is a program based on ICBT with a therapist support to treat anxiety and depression in infertile individuals. We designed "Peaceful Mind" to provide the patients with multimedia interactions that convey the core principles of CBT via the internet. The patients could access the website (www.peacefulmindme.com) and use the treatment in two ways. The therapist could register the eligible patients or the patients could get acquainted with the website by searching on the internet or through others' recommendation and register in the "*Request for treatment*" section. Subsequently, the admin contacts the patient according to the patient's information and contact number. Following the therapist's approval, a password and a username are sent to the patient and the treatment sessions start.

This website has two sections: the therapist panel and the patient panel. The patient panel is the part in which the participants can start their treatment sessions by entering their own password. The treatment sessions guide the patients step by step towards gaining the ability to get better through the self-help methods.

ICBT consisted of eight sessions and each session comprised several stages. The patient entered the treatment session and moved the pages forward step by step. The treatment steps included videos of a professional who guided the patient and talked about the ways they could help themselves. Photos and texts, as tools for better understanding, and the audio section as "guide voice" helped the patient to get through the treatment process. Some videos were prepared centered on a fictional character struggling with anxiety and depression, who tried to improve their condition with the help of this approach so that the patients could identify their problems and feel that they are not alone. Moreover, quizzes and assignments were designed to improve the patient interactions with the treatment. During the sessions, by asking questions about the content, we tried to further attract the patients' attention to the content. With the help of exercises and assignments, the patients were asked to implement the approach to their problem.

2.2. Second phase: conducting an RCT for the efficacy of "peaceful mind"

We conducted a 2-arm parallel group, non-inferiority randomized control trial between October 2020 and July 2021 in Fatemeh Zahra Infertility and Reproductive Health Research Center (north of Iran). The Ethics Committee of National Institute for Medical Research Development (NIMAD)(IR.NIMAD.REC.1398.174) and it was registered in the Iranian Registry of Clinical Trials (IRCT20110228005931N9). In addition, we obtained a written informed consent online or through paper.

2.3. Participants and recruitment

Herein, the infertile women in the waiting list of beginning the ART in the infertility center were recruited. The eligibility criteria included: 1) willingness to participate in the study; 2) 5 years of education at least; 3) 18–40 years of age; 4) meeting the criteria for probable diagnosis of depression with an interview using the Structured Clinical Interview for DSM-5 Disorders (SCID-5-CV); 5) access to computers and the internet; 6) access to a telephone always available. The participants were excluded if the following factors were reported through the clinical interviews: 1) diagnosis of bipolar disorders, schizophrenia, or suicide; 2) current substance use; 3) having undergone psychotherapy/pharmacotherapy for the treatment of anxiety/depression in less than the previous eighth weeks; 4) currently undergoing psychotherapy or pharmacotherapy for the treatment of anxiety/depression. The patients reporting severe psychiatric disorders or current suicidality were excluded and referred to a mental health service for receiving a suitable treatment.

3. Measures

3.1. Primary outcome measures

3.1.1. Beck depression questionnaire (BDI)
This scale is a 21-item self-report inventory measuring the presence and severity of depression [35]. The scores of each item range from 0 to 3; the total score, ranging from 0 to 63, is calculated by summing the scores of each item. A higher score reflects greater depressive symptoms. We used the validated Persian BDI-II version [36]. Cronbach's alpha the BDI–II–Persian was 0.87 and test-retest reliability was acceptable (r = 0.74).

3.1.2. Beck anxiety questionnaire (Bai)
The Beck Anxiety Inventory (BAI), created by Aaron T. Beck (1988), consists of 21 items and evaluates the symptoms of anxiety on a Likert ranging from 0 = not at all to 3 = severely, and the total scores ranging from 0 to 63 [37]. We used the validated Persian BAI version [38]. The Persian version of BAI proved high internal consistency (Cronbach's alpha = 0.92) and very good validity (r = 0.83, p < 0.001).

4. Secondary measures

4.1. Fertility problem inventory (FPI)

This questionnaire was created by Newton in 1999 [39]. It is a 46-item multidimensional instrument for diagnosing infertility-related problems in five subscales, namely social concern, sexual concern, relationship concern, the need for parenthood, and the rejection of a childfree lifestyle. Each item is scored on a six-point scale, ranging from 1 (strongly disagree) to 6 (strongly agree). The possible total score is 46–276; higher scores of FPI indicate greater levels of perceived stress. We used the validated Persian FPI [40]. Cronbach's alpha for all sub-scales was more than 0.70 and the overall integrity was found to be 87%.

4.2. Cognitive Therapy Awareness Scale (CTAS)

This 40-item true-false test measures knowledge about the principles and methods of CBT. The total score on the CTAS is 40. Each 10 question has four true/false statements about basic CBT principles which range from 0 to 4 [41].

4.3. Client Satisfaction Questionnaire (CSQ-8)

The Client Satisfaction Questionnaire was developed by Lasern et al. (1979) [42]. CSQ-8 is the short form of a 31-item instrument that measures the general satisfaction. This instrument consists of 8 Likert-type items ranging from 1 to 4 (1 indicates the lowest degree of satisfaction and 4 the highest).

4.4. System Usability Scale (SUS)

The System Usability Scale, developed by John Brooke (1986), is a simple, self-report scale to evaluate perceived ease of use [43]. It comprises 10 items with a 5-point Likert scale; from strongly agree to strongly disagree. To calculate the SUS score, the score of the items with odd numbers –is subtracted by 1 and the score of items with even numbers -is calculated by subtracting the score from 5. Through multiplying the sum of the scores by 2.5, the overall value of SUS is obtained. The total score could range between

0 (extremely poor usability) and 100 (excellent usability). We used the validated Persian SUS [44]. The computed Cronbach's alpha for the Persian version of SUS was 0.79.

4.5. Procedures

The assistant of the psychologist (SS author), called the infertile women and invited them to participate in the study. She assessed the patients based on the inclusion criteria. If the patients met these criteria, she invited them to have a clinical interview with the psychologist. Those with initial eligibility in primary assessment were referred to a psychologist in the center to undergo a face to-face/telephone call interview using the Structured Clinical Interview for DSM-5 (SCID-5-CV) [45]. As this work was implemented during the pandemic of COVID-19, the psychologist conducted interviews through telephone call for the patients who did not want to attend the clinic. The psychologist interviewed 146 infertile women and 86 patients were excluded (49 due to no clinical depression/anxiety, 21 due to having severe psychiatric disorders (psychotic symptoms, bipolar disorders, substance abuse), and 16 due to having attended psychotherapy sessions in the last three months and the current use of antidepressants (Fig. 1).

After being interviewed by the psychologist, the assistant of the psychologist asked the eligible women to complete the questionnaires of the study. She conducted the assessments using the DigiSurvey® platform through a link sent to the women using WhatsApp® or Telegram®. All the participants completed the questionnaires of the study, which included demographic characteristics, Beck Depression Inventory (BDI-II), Beck Anxiety Inventory (BAI), Fertility problem inventory (FPI), Cognitive therapy awareness scale (CTAS), and Automatic thoughts questionnaire (ATQ) at the baseline, in the mid-trial stage (4 weak after beginning the treatment), and the post-trial stage (8 weak after beginning the treatment). In the ICBT group, the feasibly of the program with
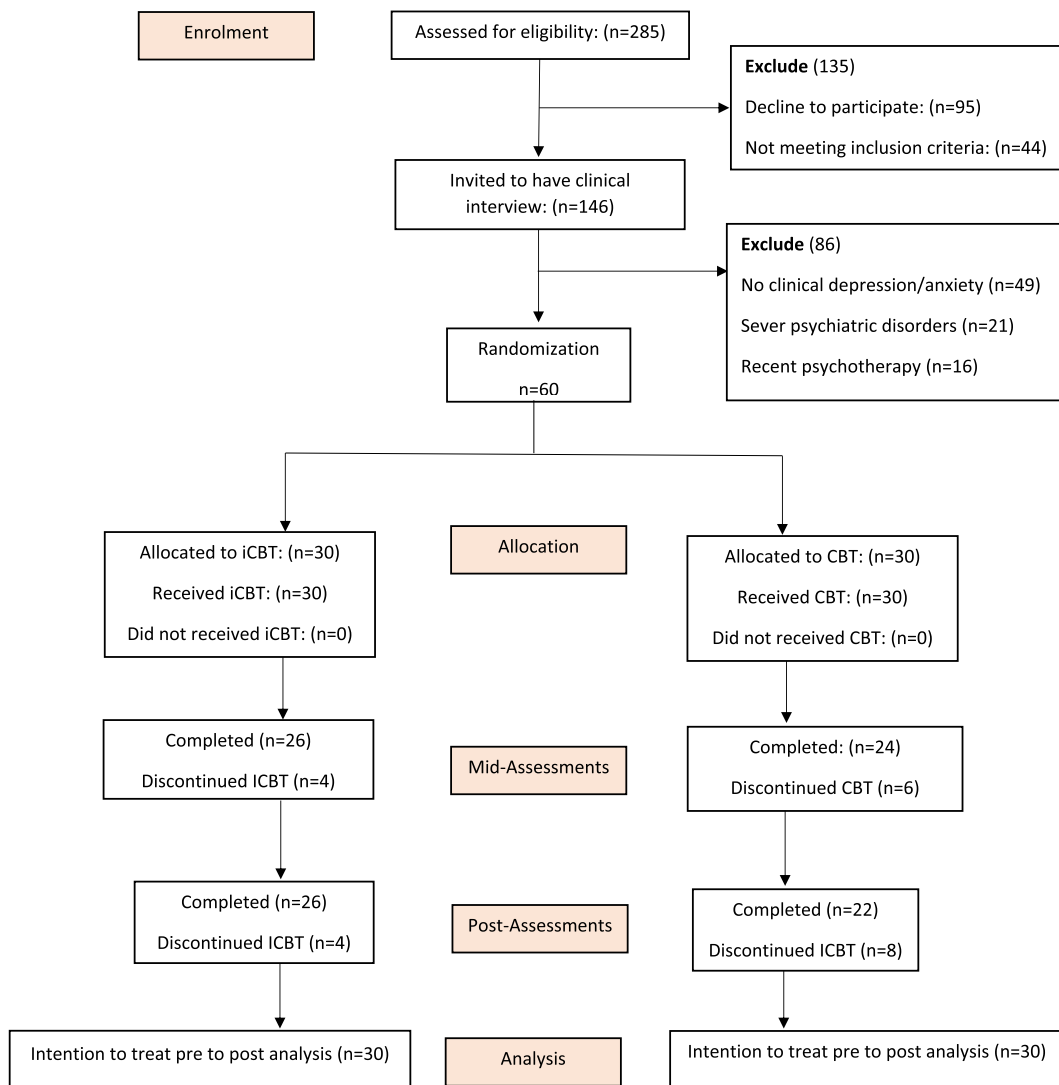

Fig. 1. Flow-chart of the participants.

System usability scale (SUS) was also assessed at the post-trial stage.

An employee of the clinic, who was not involved in the trial, completed the randomization according to a 1:1 ratio within blocks of 4 using a random number generator (www.random.org). 60 eligible participants diagnosed with depression/anxiety through diagnostic interview were randomly allocated to either ICBT (n = 30) or face-to face CBT (n = 30) interventions. On account of the nature of the intervention, group allocation was known to the participants and the investigators. However, the allocation sequences were concealed from the team of researchers. Moreover, to reduce the risk of bias, the statistician was masked during data analysis.

4.6. Treatments

Internet-based CBT. The method of ICBT used in "Peaceful Mind" was designed to integrate internet-delivered training with a therapist support. This method is a six-module multimedia program (www.peacefulmindme.com). The content of the ICBT therapist-supported program was approved by the members of the psychiatry and psychology department of Babol University of Medical Sciences. The content of ICBT was conducted according to the methods proposed by Beck et al. [46,47] and Wright et al. specifically "Good Days Ahead" program [41,48,49], focusing on psycho-education of infertility [50].

"Peaceful Mind" consists of six modules, including psycho-education, principles of CBT, restructuring techniques, behavioral techniques, changing schemas, and reviewing goals. The details of the modules are explained in Table 1. The treatment was provided to the patients in eight sessions with a duration of 50 min. The participants were required to pass one treatment session per week and practice between the sessions. In addition to the treatment sessions, psychological training and patient questions about infertility were provided in the library section of the website (Supplementary1, Screenshot of the peaceful mind).

The ICBT guided-therapist was conducted by a female psychologist (author MF) 25 min weekly via telephone/Whatsapp. The therapist had enough experience in ICBT-therapist approach. The therapist had a telephone/Whatsapp session on a scheduled time and reviewed the materials of ICBT modules and assignments. Additionally, the therapist answered the questions and solved problems of the patients.

A female assistant (author SS), who was trained in the ICBT approach before the trial, helped the therapist in the telephone/Whatsapp contacts. The assistant replied to the patients within 24 h on weekdays. She supported the patients to do the assignments, provided feedback on homework assignments, and answered the patients about the contents. She encouraged the patients to contact the therapist if they wanted to have any clarification regarding the therapy. The assistant notified the patients a "remind message" with a short mobile text message (SMS)/Whatsapp to log on to the treatment session every week. She also sent the patients a short mobile text message (SMS) whenever they had not logged on to the treatment platform for one week. If the patients did not participate in the online session, the assistant called them, checked the problems, and reminded and encouraged them to continue the treatment as soon

Table 1
Session's content and exercise.

Module	content	exercise
Psycho-education for infertility	Infertility Causes of infertility in men/women Treatments in infertility Sources of stress in infertility	–
Introduction to principles of CBT	Introduction Role of thoughts and emotions in pain Understanding automatic thoughts relationship between thoughts and emotions recognize automatic thought	Recording Positive Thoughts Recording Negative Thoughts Changes in negative Thinking Recording Positive and Negative Thoughts in infertility
restructuring methods	starting to change automatic thoughts linking thought and feelings Common Cognitive errors Cognitive errors in infertility Evaluating and generating rational/adaptive thoughts	First 4 Steps of the Thought Change Record (TCR) TCR in infertility Identify Cognitive Errors Identify Cognitive Errors in infertility First 5 Steps of the Thought Change Record (TCR) TCR in infertility Evidence gathering Finding rational/adaptive thoughts Thought Change Record (TCR)
behavioral techniques	Behavioral patterns activity planning to have more pleasurable days exercises to overcome procrastination	Daily record of activity Choose pleasant activity goal Daily record of activity for infertile women Understanding procrastination Step-by-Step
Changing Schemas	identifying the schemas (core beliefs) that control your self-esteem identifying the schemas related to infertility Changing negative core beliefs	Recording Negative Schemas Recording Positive Schemas Recording Negative Schemas In infertility Changing Schemas
Reviewing goals	Relapse prevention overview of sessions future plans for coping with problems in your life future plans for coping with infertility problems in your life	Review the assignments of the previous sessions Negative Schema Update Negative Schema Update for infertility

as possible.

Face-to- face CBT. This treatment was conducted by a female psychologist (author MF) through face-to-face individual sessions on a weekly basis, each for 50 min, for a period of 8 weeks. Moreover, a female assistant (author SS) helped the psycho therapist in the sessions. The assistant attended psycho-education of the patients, supported the patients to do assignments, and provided feedback on homework.

The contents of face-to-face CBT were the standard CBT based on the approach of Beck et al. [46,47] focusing on psycho-education of infertility [50]. The contents of CBT and ICBT were the same in psycho-education, content of the sessions, and the assignments.

4.7. Sample size

The trial had two primary outcomes, including depression and anxiety being measured within 8 weeks of the intervention. The sample size was calculated using the predetermined marginal value in depression scaled with BDI from the existing literatures and expert knowledge [51], which was 1.5 comparing the face-to-face intervention to the internet-based CBT group. For this difference in depression, with an SD of 1.93 for each intervention group, a power of 80%, and an alpha of 5%, 28 women were needed in each arm. Taking into account the possible dropouts, we decided to include 30 participants per group, with the assumption of 5% attrition of the participants.

4.8. Statistical analysis

To compare the adherence of the treatment, Chi Square test was utilized. Independent *t*-test was applied to compare the mean of satisfaction treatment scores between the two groups. Chi-square tests and independent t tests were used to compare the differences between the baseline characteristics of the subjects who completed the trial to those who did not. As the baseline characteristics of 60 people in the pre-trial stage were different from those who completed the post-trial stage (48 persons), intention to treat (ITT) analysis was conducted for the outcomes. The primary and secondary outcomes were estimated using multiple imputation method for the patients who either did not comply the treatments in both intervention groups or were loss to follow-up.

The 95% confidence interval (95% CI) of the mean, which was different between the two intervention groups, was compared to the marginal value of 1.5 for BDI [52]. If the lower bound of the 95% CI meets the marginal value, you can try to endow the effect of the internet-based CBT with a non-inferior interpretation. The effectiveness of the two intervention groups was measured through eta squared effect size calculated using repeated measures analysis of variance. The value of lower than or equal to 0.06 was considered as a small size and medium. All of the alternative hypotheses were two-sided, except for the non-inferior one, which was one-sided. STATA version 15 was used for all the statistical analyses (Stata Corp., College Station, TX).

Table 2
Characteristics of the study population.

variables	CBT (n = 30)	iCBT (n = 30)	Overall (n = 60)
Age, mean (SD)	34.73 (4.69)	30.70 (5.44)	32.72 (5.43)
Education, N (%)			
Primary school	5 (16.7)	5 (16.7)	10 (16.7)
≥High school	25 (83.3)	25 (83.3)	50 (83.3)
Job, N (%)			
Unemployed	22 (73.3)	19 (63.3)	41 (68.3)
Employee	8 (26.7)	11 (36.7)	19 (31.7)
Age of husband, mean (SD)	38.57 (7.50)	33.40 (5.75)	35.98 (7.12)
Education of husband, N (%)			
Primary school	15 (50)	10 (33.3)	25 (41.7)
≥High school	15 (50)	20 (66.7)	35 (58.3)
Duration of marriage, mean (SD)	9.03 (4.90)	5.70 (3.37)	7.37 (4.50)
Duration of infertility, N (%)			
≤4	8 (26.7)	18 (60)	26 (43.3)
≥5	22 (73.3)	12 (40)	34 (56.7)
Caused of infertility, N (%)			
Female factors	2 (6.7)	10 (33.3)	12 (20)
Male factors	11 (36.7)	6 (20)	17 (28.3)
Female and male factors	10 (33.3)	10 (33.3)	20 (33.3)
Unknown	7 (23.3)	4 (13.3)	11 (18.3)
Number of ART, mean (SD)			
IUI	0.97 (1.47)	1 (1.39)	0.98 (1.42)
IVF	0.40 (0.72)	0.33 (0.95)	0.37 (0.84)

Abbreviations: ICBT, internet-based cognitive behavioral therapy; CBT, based cognitive behavioral therapy.

5. Result

5.1. Study flow and baseline participant characteristics

Out of the 30 participants in the ICBT group, four (%13.3%) dropped the trial (three people before the mid-trial and one person after that). Out of the 30 participants in the CBT group, eight (%26.6%) dropped the trial (six people before the mid-trial and two after that) (Fig. 1).

Table 2 depicts the characteristics of the participants. The mean (SD) age of the participants was 32.72 (5.43) years (range = 21–44). The majorities of the subjects had graduated from high school or above (83.3%) and were housewives (68.3%). Women's husbands with a mean (SD) age of 35.98 (7.12) (range = 25–70) were mostly graduated from high school or above (58.3%). The mean (SD) marriage duration was 7.37 (4.50), and 56.7% of the participants experienced infertility for five years or above. Among the causes of infertility, the prevalence of female factor was 6.7%, male factor was 36.7%, male and female factor was 33.3%, and unknown factor was 23.3%. The mean (SD) numbers of IUI and IVF were 0.98 (1.42) and 0.37 (0.84), respectally. There were no significant differences between the ICBT and CBT group regarding the demographic characteristics, as reported in Table 2.

6. Primary outcome

6.1. Program activity and support

As described in Table 2, two groups of the treatment (ICBT versus CBT) were matched as the baseline characteristics. 48 participants (80%) completed the study at the post-trial stage (22 in CBT versus 26 in ICBT). The baseline characteristics of 60 individuals in the pre-trial stage were not different with those who completed the post-trial stage (48 persons).

The participants in the ICBT group completed a mean (SD) of 7.97 (2.02) of nine modules (range: 0–9); 23 (76.7%) completed all the nine modules, two (%6.7) completed three modules, two (%6.7) completed four modules, one (%3.3) completed five modules, one (%3.3) completed six modules, and one (%3.3) completed seven modules.

6.2. Within-group effectiveness of treatments on depression and anxiety

Table 3 presents the outcome comparisons within groups and between the two groups. For the ICBT group, depression scores of women decreased significantly from the pre-to post-trial stages (the mean differences −4.95, CI 95% −9.07 to −0.83). However, no significant differences in depression scores of the participants revealed from pre-trial stage to the mid-trial (the mean differences

Table 3
Group comparisons before and after intervention.

Measure group	Intervention, mean (SD)			Within-group		Eta effect size for time	Between-group		Eta effect size for intervention
	Pre-test (T0)	Mid-test (T1)	Post-test (T2)	Mean diff (CI 95%) T0–T1	Mean diff (CI 95%) T0–T2		Mean diff (CI 95%) T0–T1	Mean diff (CI 95%) T0–T2	
Depression									
ICBT	19.13 (7.80)	18.50 (7.54)	14.17 (9.57)	−0.69 (−4.30, 2.90)	−4.95 (−9.07, −0.83)	0.06	−1.34 (−6.33, 3.64)	−4.79 (−10.81, 1.23)	
CBT	24.79 (8.90)	22.32 (9.22)	15.04 (11.34)	−2.04 (−5.64, 1.55)	−9.75 (−14.32, −5.17)				0.002
Anxiety									
ICBT	13.85 (9.78)	10.51 (7.75)	9.80 (10.09)	−3.53 (−6.05, −1.01)	−4.04 (−7.34, −0.74)		−0.82 (−6.90, 5.25)	−4.15 (−9.52, 1.22)	
CBT	20.73 (10.90)	16.29 (10.83)	12.54 (9.66)	−4.36 (−10.04, 1.32)	−8.19 (−12.58, −3.79)	0.14			0.02
Infertility stress									
ICBT	152.77 (34.12)	152.56 (40.52)	141.55 (36.60)	−2.24 (−15.08, 10.60)	−11.22 (−23.78, 1.33)		9.49 (−6.45, 25.43)	7.51 (−8.91, 23.94)	
CBT	156.03 (32.50)	163.28 (27.42)	152.32 (36.67)	7.25 (−2.78, 17.28)	−3.70 (−14.78, 7.37)	0.05			0.04
Cognitive therapy awareness									
ICBT	21.18 (4.76)	–	24.75 (4.07)	–	3.56 (1.88, 5.24)	–	–	−1.6 (−4.00, 0.80)	0.05
CBT	20.93 (3.50)	–	22.90 (4.43)	–	1.96 (0.17, 3.76)				

Abbreviations: ICBT, internet-based cognitive behavioral therapy; CBT, based cognitive behavioral therapy.
Range of scores: depression, 0–63; anxiety, 0–63; infertility stress, 46–276; cognitive therapy awareness, 0–40.

−0.69, CI 95% −4.30 to 2.90). Anxiety scores of women decreased significantly from the pre-to post-trial stages (the mean differences −4.04, CI 95% −7.34 to −074). In addition, the mean differences of anxiety scores of the subjects improved significantly from the pre-trial stage to the mid-trial (−3.53, CI 95% −6.05 to −1.01).

For the CBT group, depression scores of women improved significantly from the pre-to post-trial stages (the mean differences −9.75, CI 95% −14.32 to −5.17). However, there were no significant differences in depression scores of the participants between the pre-trial and the mid-trial (the mean difference −0.69, CI 95% −4.30 to 2.90). Anxiety scores of women improved significantly from pre-to post-trial stages (the mean differences −8.19, CI 95% −12.58 to −3.79). However, no significant differences were observed in their depression scores between the pre-trial stage and the mid-trial (the mean differences −2.04, CI 95% −5.64 to 1.55).

6.3. Between-group effectiveness of treatments (ICT vs CBT) on depression and anxiety

The interaction effects of group and time were not significant for the depression scores between the pre-trial stage and the mid-trial and between the pre-trial stage and the post-trial. The estimated mean difference (95% CI) on the depression scores between the two groups (ICBT vs CBT) was −1.34 (CI 95% = −6.33to 3.64) in the mid-trial and −4.79 in the post-trial stage (CI 95% = −10.81to 1.23). Thus, the upper limit of the 95% CI was not below the pre-specified non-inferiority margin of 1.50 points for depression scores (BDI-II).

The interaction effects of group and time were not significant for anxiety scores between the pre-trial stage and the mid-trial and between the pre-trial stage and the post-trial. The estimated mean difference (95% CI) on the anxiety scores between the two groups (ICBT vs CBT) was −0.82 (CI 95% = −6.90 to 5.25) in the mid-trial and −4.15 in the post-trial stage (CI 95% = −9.52 to 1.22). Thus, the upper limit of the 95% CI was not below the pre-specified non-inferiority margin of 2.0 points for anxiety scores (BAI).

6.4. Secondary outcomes

Infertility stress: For both ICBT and CBT groups, the within-group estimated mean differences for infertility stress revealed no significant improvement neither from the pre-trial stage to the mid-trial nor from the pre-to post-trial stage.

The interaction effects of group and time were not significant for infertility stress between the pre-trial stage and the mid-trial and between the pre-trial stage and the post-trial. The estimated mean difference (95% CI) on the infertility stress between the two groups (ICBT vs CBT) was 9.49 (CI 95% = 95% −6.45 to 25.43) in the mid-trial and 7.51 in the post-trial stage (CI 95% = -8.91 to 23.94). Thus, the upper limit of the 95% CI was not below the pre-specified non-inferiority margin for anxiety scores (FPI).

Cognitive Therapy Awareness Scale (CTAS): For the ICBT group, the mean scores of cognitive therapy awareness increased significantly from the pre-to post-trial stage (the mean differences 3.56, CI 95% 1.88 to 5.24). For the CBT group, the mean scores of cognitive therapy awareness also improved significantly from the pre-to post-trial stage (the mean differences 1.96, CI 95% 0.17 to 3.76).

The estimated mean difference (95% CI) on the scores of cognitive therapy awareness (−1.6, CI 95% = 95% −6.45 to 25.43) showed no significant differences between the ICBT and CBT in the post-trial stage.

Treatment satisfaction: We assessed the treatment satisfaction with Client Satisfaction Questionnaire (CSQ-8). The mean (SD) CSQ-8 score among the participants who completed at least five sessions was 28.20 (2.29) in the CBT group and 25.06 (4.18) in the ICBT group. There was no significant difference concerning the treatment satisfaction between the ICBT and CBT groups. In addition, patient adherence to treatment, for those who completed the trial, in the ICBT group (26/30, 86.6%) was the same as that in the face-to-face CBT (22/30, 73.3%) (P = 0.33).

System Usability Scale (SUS): The patients scored the usability of "Peaceful Mind" to be 67.07 (SD = 17.23, range 1–100). Hence, the mean of the usability of the program was higher than the moderate level. About 73.3% of the participants (22/30) stated that overlay website was user friendly and that they could trust it. About 80% of those who completed the ICBT program were satisfied with the program and stated that they would return to the treatment if they seek help again. Furthermore, 88% of the participants reported that if a friend needed help with the same conditions, they would recommend the treatment.

7. Discussion

The current study confirmed the acceptability, feasibility, and effectiveness of "Peaceful Mind" ICBT regarding the treatment of depression or anxiety disorders in the Iranian population. In addition, the results demonstrated that ICBT was non-inferior to face-to-face CBT concerning the improvement of all the outcome variables.

In term of feasibility of "Peaceful Mind" ICBT, 73.3% of the cases stated that overlay website was user friendly. The obtained mean system usability (67.07 ± 17.23) was higher than that in another study (65.1, SD = 13.37) [53] whereas it was lower than that in another report (M = 71.16, SD = 18.97) [54]. The usability of the internet-based interventions is an important factor in successful implementation and patient engagement [55]. Certain problems of the patients with ICBT were the low speed of the internet, not being able to contact the therapist after the sessions immediately, and not being able to load the footages fast enough. Since "Peaceful Mind" is the first ICBT in Iran, the lack of high mean of feasibility is not surprising. It could be recommended that "Peaceful Mind" ICBT be improved in future research in order to provide further usability for patients.

In terms of acceptability, 23 participants (76.7%) completed the entire nine-module program within the 8-week treatment window. The completion rate of ICBT in this study was comparable with a study conducted by Wright et al. (%78.1) [41]. Moreover, Patel et al. (2018) reported that 70% of the participants of ICBT completed the entire 10-module program [56]. In addition, about 80% of our participants who completed the ICBT program were satisfied with the program and stated that they would return to the treatment if

they seek help again. Our subjects were found to have higher satisfaction (CSQ-8 scores) than those in a previous study on people with coronary artery disease (M = 20.6, SD = 0.88) [57], which is in line with previous studies based on Indonesian University Students (M = 25.8, SD = 3.40) [53]. Certain assumptions were proposed herein to explain high satisfaction of the ICBT program. Primarily, "Peaceful Mind" ICBT is an integrated internet-delivered training with a therapist support. Previous studies have revealed that ICBT with a therapist support resulted in further satisfaction than ICBT without a therapist support [58]. Secondly, the inclusion criteria in our study were women who accessed computer and the internet. The present work selected the women who had further tendency towards computer/internet survey; therefore, the participants could be more satisfied with ICBT. Additionally, getting informed consent process during the recruitment could have contributed to a higher interest in continuing the program.

Interestingly, our findings demonstrated that the patients' adherence to "Peaceful Mind ICBT" was high. The adherence rate of our study (86.6%) was higher than that in the study by Rahmadiana with an adherence rate of 52% [53]. The dropout rate in this study (13.4%) appeared to be the same as that reported by Andersson et al. (2011) (12.5%) [31] and lower than that reported by Patel (30%) [56]. We also found that adherence to treatment in the ICBT group was equal to that in the CBT group. For explanation of high adherence of the participants in the ICBT program, some assumptions were considered. Primarily, our ICBT program was supported with a therapist and was not a self-help program. A report of a self-help program, Mood Gym ICBT, showed poor adherence to treatment. About 4.3% of the users completed all the five modules of the program [59]. Secondly, all the participants met a clinical psychologist to have clinical interviews and be assessed concerning the depression/anxiety disorder. Hence, the ICBT program was supported with an additional session by a mental specialist before trial started and delivered the interne treatment.

Our results revealed that both ICBT and CBT significantly improved the depression and anxiety of the infertile women from the pre- to post-trial stages. In line with our results, Rahmadiana et al. (2021) reported the efficacy of ICBT, who studied 50 Indonesian students with mild to moderate depression, anxiety, or both, based on a nine-item Patient Health Questionnaire (PHQ-9 score >4), seven-item Generalized Anxiety Disorder (GAD-7 score >4), or both. The students received I-AiMentalWELLness Intervention. The basis of the program was the principles of the CBT. Rahmadiana et al. concluded that ICBT significantly reduced both depression and anxiety following seven weeks of treatment [53]. Furthermore, some other ICBT programs were reported to be efficient for reducing anxiety and depression [60,61]. In contrast, a meta-analysis reported an insignificant effect size (0.27) for ICBT programs [62].

Note that in this study, "Peaceful Mind" ICBT was as effective as face-to-face CBT in the treatment of depression and anxiety. As this study is the first RCT to compare the effect of ICBT to that of face-to-face CBT concerning the improvement of depression/anxiety in infertile women, we could not find any research to compare our results. Thus, we documented the research comparing the effect of ICBT to that of CBT in patients without infertility problems. Beukes et al. (2018) compared the efficacy of ICBT versus face-to-face CBT in the improvement of tinnitus distress. They concluded that ICBT was effective as face-to-face CBT tinnitus-related difficulties [63]. In agreement with our results, some evidence supports that ICBT has the same effect as face-to-face CBT for the treatment of depression [29,30]. Some studies have also reported the equal effectiveness of ICBT with that of CBT for reducing both depression and anxiety symptoms [64–66]. It is important to explain how ICBT improves the depression and anxiety as same as CBT. It may be attributed to the integration of ICBT with a therapist support. Additionally, the content of the sessions, psycho-education, and the assignments of ICBT were the same as those in face-to-face CBT. Finally, ICBT was conducted by a female psychologist and a co-assistant, who also conducted the face-to face CBT.

In our findings, infertility stress did not change significantly in both ICBT and CBT groups. Similarly, two randomized controlled trials, using an online intervention, reported no significant changes in infertility-specific stress in women dealing with infertility [33, 67]. It is important to explain why ICBT and CBT did not improve the infertility stress in women. It may be assigned to the treatment approach. We used a model of psychotherapy emphasizing depression and anxiety, rather than infertility stress. Although we had psycho-education on infertility, we did not emphasize childless anxiety of the women.

It was found that the ICBT achieved comparable scores on the improvement of cognitive therapy awareness compared with the CBT treatment. In line with our results, Calero et al. (2021) reported that patients who had undergone ICBT with and without guidance sessions showed a statistically significant improvement in automatic thoughts measure [68]. Similar to our results, previous studies have reported no significant differences between ICBT and CBT in the improvement of automatic thoughts of subjects [33,67].

7.1. Study strength and limitations

To the best of our knowledge, this is the first research to examine the development, feasibility, and acceptability of ICBT in Iran. Another major strength of this work was the fact that this was the first randomized clinical trial study to compare the effectiveness of ICBT to that of face-to-face CBT in infertile women.

While these results are promising, there are certain limitations to be noted. Initially, the ICBT program developed in this study combined both therapist support and internet-based model; thus, the effect of separate ICBT could not be clarified. Moreover, as this was a preliminary study of ICBT in Iran on infertile women, the participants were depressed/anxious and the therapy was mixed for anxiety/depression disorders. Further research is required to focus on the development of ICBT programs for the treatment of depression and anxiety separately. Not only that, small sample size, gender specific, infertile population, and the absence for the follow-up could be noted as other limitations. Further studies are required to compare the effectiveness of ICBT to that of CBT with a larger sample size in both men and women, with long-term follow-up periods. Eventually, the results were obtained from one center with specific infertility-associated problems. It could be suggested that further multicenter studies be conducted on the feasibility and efficacy of ICBT in more diverse groups with depressive or anxiety disorders in order to improve the generalizability of these preliminary results. In addition, the effect of ICBT and other internet-based psychotherapies improving the anxiety and depression should be further investigated.

More research is also warranted to confirm the findings of this study, to test the potential maintenance of the treatment in a long follow-up and improve the feasibility and acceptance of "Peaceful Mind" ICBT program. Furthermore, this promising feasibility study could be suggested to be followed and the effectiveness of the ICBT could be further investigated in order to treat depression and anxiety in the people in Iran. Future RCT studies with a large sample are of great necessity prior to making "Peaceful Mind" ICBT publicly available in Iran.

8. Conclusion

This study is the first to develop an ICBT program with a therapist support for the patients with depression and anxiety in Iran. "Peaceful Mind" ICBT was found to be feasible and accessible for delivering the treatment to the patients. The participants of the "Peaceful Mind" ICBT were highly motivated and satisfied with the program. In addition, the results confirmed that the efficacy of "Peaceful Mind" ICBT for improvement of depression and anxiety was equal to that of CBT and provided an alternative for depressed/anxious patients who are unable to obtain face-to-face CBT. "Peaceful Mind" ICBT program may also increase the treatment accessibility for depressed/anxious individuals who avoid seeing a therapist in Iran. The findings of this preliminary examination on the development and efficacy of "Peaceful Mind" ICBT warranted replications of future research for testing ICBT in other patients in Iran.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contribution statement

Farzan Kheirkhah: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.
Mahbobeh Faramarzi; Shiva Shafierizi: Conceived and designed the experiments; Performed the experiments; Wrote the paper.
Zahra Basirat: Contributed reagents, materials, analysis tools or data; Wrote the paper. Mohammad Chehrazi: Analyzed and interpreted the data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e15760.

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