Original Article

Pharmacotherapy or Psychotherapy? Selective Treatment Depression in The Infertile Women with Recurrent Pregnancy Loss: A Triple-Arm Randomized Controlled Trial

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Abstract

Background: Recurrent pregnancy loss (RPL) and infertility are associated with significant psychiatric complications. The study aimed to investigate the effectiveness of cognitive behavioral therapy (CBT) and sertraline in the treatment of in depression, anxiety, and infertility stress of depressed infertile women with RPL in comparison with usual care.

Materials and Methods: A triple-arm randomized controlled trial was carried out on the 60 depressed infertile women with RPL, a population of Infertility Center of Babol city, Iran, who were randomly assigned into three groups: pharmacotherapy with sertraline (n=20), psychotherapy with CBT (n=20), and a usual care as control group (n=20). The participants of psychotherapy received CBT sessions (90 minutes each) over 10 weeks. The participants in the pharmacotherapy group took 50 mg/day sertraline daily for 22 weeks. Outcomes were assessed using the Beck Depression Inventory (BDI-II), fertility problem inventory (FPI), and State-Trait Anxiety Inventory Form Y (STAI-Y) at the beginning of the trial, 10-weeks post-trial, and three months of follow-up. Using statistical package for the social sciences (SPSS) software, data were analyzed.

Results: CBT considerably reduced the depression symptoms more than sertraline with a moderate effect size at the post-trial (g=0.11, 95% CI: -0.03 to -0.50). Sertraline showed reduced the scores of state-anxiety more considerably in comparison with control group by a large effect size of post-trial (g=-1.04, 95% CI: -1.70 to -0.38). CBT reduced the total scores of FPI more considerably than sertraline, with a large, small size at follow up-trial [95% CI=-0.03(-0.65, -0.58)]. Both CBT and sertraline were superior to the control group in reducing depression and infertility stress.

Conclusion: Depression and infertility stress diminished under CBT and sertraline in depressed infertile women with RPL, with a significant advantage of CBT. Sertraline was superior to CBT in reduction of anxiety (registration number: IRCT201304045931N3).

Keywords: Anxiety, Cognitive Behavior Therapy, Depression, Infertility, Recurrent Early Pregnancy Loss

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Introduction

Recurrent pregnancy loss (RPL) is defined as two or more consecutive miscarriages before gestation week 22. It has been estimated to be prevalent in approximately 5% of clinically diagnosed pregnancies (1, 2). An overlap etiology and a number of collaborative pathologies were shown for infertility and RPL (3). Although, the risk of RPL increases in the women who are conceived with assisted-reproductive technology (ART) (4). Infertile females experience some psychological problems, including poor quality of life, depression, anxiety, sexual dysfunction function, and marital dissatisfaction (5-7). A recent meta-analysis reported 44.32% depression prevalence in the infertile women (8). Also, infertile women are at higher risk of psychological problems than infertile men (9). Women with RPL suffer from many psychiatric morbidities such as depression, anxiety, complicated grief, and suicide (10). Also, the psychiatric morbidity of infertility may be exacerbated by the RPL (11, 12).

Whilst the evidence for the effect of psychotherapy and pharmacotherapy in the mental health improvement of infertile women is robust, support for their use in infertile women with RPL is sparse. Most research has focused

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only on the infertile women who experiencing depression after *in vitro* fertilization (IVF) failure (13), while few studies have evaluated psychotherapy for depressed infertile women with RPL. To the best of our knowledge, no randomized controlled trial study has explored the effect of psychotherapy for women with RPL; it is unclear whether these findings can be generalized to depressed women with RPL. Nakano et al. (14) reported that cognitive behavioral therapy (CBT) reduced anxiety or depression scores in the 14 women with RPL. Patel et al. (15) reported that mindfulness psychotherapy improved the emotional adjustment in an infertile couple with RPL. Also, some research reported that CBT was useful for patients with a single perinatal loss (16, 17). Although, some research has proposed pharmacotherapy during pregnancy as a risk factor of pregnancy loss (18, 19). There are studies that recommended preconception counseling by psychologist/psychiatrists or antidepressants treatment for RPL women with severe depression (20, 21). To our knowledge, no study has been published to date that compare the effectiveness of psychotherapy and pharmacotherapy for depression treatment in the women with RPL.

We designed this study to investigate the effect of psychotherapy and pharmacotherapy in RPL women to compare the effect of the two methods of depression treatment in women with RPL. To the best of our knowledge, this is the first three arm randomized controlled trial that compares the effectiveness of CBT with sertraline for the treatment of depression in the infertile women with RPL. The hypotheses of the study were to examine: i. Whether CBT or sertraline is superior than usual care in reducing the score of depression in depressed infertile women with RPL, ii. Whether CBT or sertraline is superior than usual care in lowering the score of anxiety or infertility stress of depressed infertile women with RPL, iii. Which approach, pharmacotherapy or psychotherapy, is superior for mitigating the symptoms of depression, anxiety, and infertility stress among depressed infertile women with RPL.

Materials and Methods

Study type, setting, and duration

A triple-arm parallel-group randomized controlled trial design was conducted from November 2016 to December 2019 in the Fatemeh Zahra Infertility and Reproductive Health Research Center (Mazandaran, Iran), a single university-affiliated IVF center. The trial protocol was approved by the Ethics Committee of Babol University of Medical Sciences, Mazandaran, Iran and was registered in the Iranian Registry of Clinical Trials (IRCT201304045931N3). A written informed consent was obtained before the participants.

Study participants and procedure

All participants were recruited from Recurrent Abortion Clinic of the center Fatemeh Zahra Infertility and Reproductive Health Research Center. Eligibility criteria were included: i. Two or more consecutive miscarriages, ii. At least 5 years of education, iii. 18-40 years of age, iv. Meeting the criteria for probable diagnosis of depression with interview using the Structured Clinical Interview for DSM-5 Disorders (SCID-5-CV), v. Not undergoing fertility treatment until 6 months afterward. The participants were excluded if through clinical interviewing, the psychologist reported: i. Diagnosis of severe depression, bipolar disorders, schizophrenia, or suicide, ii. Having psychotherapy in the last three months, and current use of antidepressants. The excluded patients who suffered from severe mental disorders were referred to a psychiatrist to receive a suitable treatment.

A midwife assessed the inclusion criteria for the patients. If the patients met the inclusion criteria, they were invited to study and completed the demographic questionnaire. Women with initial eligibility in primary assessment were referred to our psychologist to receive a face to-face interview based on Structured Clinical Interview for DSM-5 Disorders (SCID-5-CV) (22). All participants completed three questionnaires, including the Beck Depression Inventory, second edition (BDI-II), Fertility Problem Inventory (FPI), and State-Trait Anxiety Inventory Form Y (STAI-Y) at baseline, 10-weeks post-trial, and three months of follow-up.

Sample size calculation

Available sampling was performed on the infertile women who referred to our center. As we could not find any research comparing the efficacy of CBT and sertraline on the infertile women with RPL, power calculation was performed based on published RCT of CBT and other pharmacotherapies in the infertile women (14, 23). Also, we conducted a pilot study to calculate the differences between the three groups of the study. To detect the smallest differences, 2.5 on the BDI-II, the minimum sample size for each group (α=0.05, power of 80%) was 16 participants. Thus, we recruited a minimum volunteer of 60 participants, with an attrition risk of 20%.

Randomization

Sixty depressed infertile women with RPL were divided randomly into three groups: pharmacotherapy with sertraline (n=20), psychotherapy with CBT (n=20), and a usual care as control group (n=20). Randomization was completed by an independent midwife according to 1:1:1 ratio using a computer random number generator. Also, allocation randomization was done using sequentially numbered sealed opaque envelopes and concealed from the researcher. The midwife assigned the participants manually and informed them via phone call. One of the study coordinators who was unaware of the trial allocation or the recruitment of the participants, evaluated the treatments.

Study interventions

Psychotherapy group

This experimental group received CBT enhanced with

Functional Analytic therapy (FACBT). Kohlenberg and Tsai (24) introduced FACBT to enhance the focus on the client-therapist relationship and to gain a broader insight into the cause of the problem and treatment. This model includes seven specific enhancement techniques the CBT therapist can use to address the needs of the patients. The seven techniques include expanded rationale, greater use of the patient-therapist relationship, employing case conceptualization, noticing and recognizing Clinically Relevant Behavior (CRB), asking questions to evoke CRBs, increasing self-awareness to detect CRBs, and applying modified thought records.

A female psychologist, who was expert in infertility branch, conducted the sessions. Psychotherapy was conducted in ten group sessions (90 minutes each) over 10 weeks. Each group consisted of 10 participants. The psychotherapy treatment was based on FACBT (24) as well as five domains of specific infertility stress (25). Table 1 summarized the contents of the sessions.

Pharmacotherapy group

The patients were visited at baseline as well as 2, 6, 10, 16, and 22 weeks post-trial for adjusting the medication and recording the symptoms plus adverse events. Also, there were optional supplementary visits or telephone contacts at any time.

Sertraline (Abidi Pharmaceutical Co., Tehran, Iran) treatment was begun at 50 mg/day. Dose changes were based on the response and side effects. If the symptom reduction was achieved, patients continued the initial dose of the sertraline. However, if the symptoms were not mitigated, the dose could gradually be raised to a maximum of 200 mg/day.

Usual care group

Participants of this group received usual care of the infertile without any psychological support.

Study outcomes

Primary outcomes

Beck Depression Inventory, second edition

This scale is a 21-item self-report inventory measuring the severity of depression. Each item is scored on a four-point Likert scale, ranging from 0 to 3. Total scores range 0-63 with higher scores indicate more severe depressive symptoms (26). We used Persian validated BDI-II (27). The Persian version of the BDI-II had high internal consistency (Cronbach's alpha=0.87 for) and acceptable reliability of test-retest (r=0.74).

Fertility problem inventory

This scale was developed by Newton to assess infertility stress (27). It consists of 46 questions. Each item is scored on a six-point Likert scale, ranging from 1 (strongly disagree) to 6 (strongly agree). Some items have reversed scores. The total score of FPI ranges from 46 to 276, where higher scores indicate higher levels of infertility stress. The FPI includes five subscales: social concern (worry about comments of family or friend about her infertility), sexual concern (reduction or difficulty of sexual arousal or enjoyment), relationship concern (worry of talking about infertility with relatives or friends), rejection of parenthood (negative view of life without child), and the need for parenthood (considering parenting as essential goal of life) (25). We used the Persian validated FPI. The validity of the Persian version of FPI was high for all domains (Cronbach's alpha coefficient 70%) (28).

State-Trait Anxiety Inventory Form Y

This scale that first developed by Spielberger et al. (29), is one of the most widely used instruments for capturing anxiety. The scale provides two different components of anxiety: state and trait. This study used the anxiety state component that includes 20 items answered on a 4-point Likert scale. The possible scores range from 20 to 80. We used Persian validated STAI-Y. The Cronbach's alpha for internal consistency of the Persian version of STAI-Y was 0.846 for state anxiety and 0.886 for trait anxiety. Also, the reliability and internal consistency were good (30).

Secondary outcomes

The secondary outcomes included treatment compliance and treatment satisfaction. Treatment compliance for psychotherapy group was defined as the mean number of attendance of the participants in the CBT sessions (from 10 sessions). Treatment adherence for pharmacotherapy was defined as the mean number of formal contact sessions with a psychiatric (from 5 sessions through phone or visit in our infertility clinic). For treatment satisfaction, the participants answered to a question and rated their feeling about the program from 1 (very low satisfaction) to 5 (very high satisfaction).

Statistical analysis

To examine participants' demographic characteristics, cross-tabulations stratified by three groups were used. ANOVA tests were applied to examine group differences in clinical characteristics at baseline. Also, t test and Chi Square test were applied to examine differences in adherence or satisfaction between the CBT and sertraline groups.

We used intention-to-treat analysis to manage the missing outcomes via multiple imputation chained technique (MICE). For the participants, linear mixed models with random intercepts, time, treatment group, and time-group interaction as fix factors were used to estimate each outcome measure in the our groups. Pairwise contrasts were used to compare group differences in the pre-to-post and pre-to-follow-up outcome scores. Also, pooled standard deviation adjusted for sample size (Hedges' g) was employed to examine the effect sizes. The effect sizes were defined as small (g=0.20), medium

(g=0.50), and large (g=0.80) (31). The data were analyzed using statistical package for the social sciences (SPSS) software version 18.0 (SPSS Inc., Chicago, IL., USA). We considered P<0.05 as significant.

Results

Baseline demographic and clinical characteristics

Of 60 women who entered the trial, 50 completed the trial from baseline to post-trial and follow-up (CBT group: n=19, sertraline group: n=13, control group: n=18). Figure 1 reveals the recruitment of the participants from the beginning of the study to post-trial and follow-up.

Table 2 describes the demographic characteristics of the participants in three groups of the trial. The women, aged 31.7 years (± SD=5.9). The majority of them had high school or university level of education. There were no significant differences with respect to age, education, infertility duration, and the number of miscarriages among these three groups.

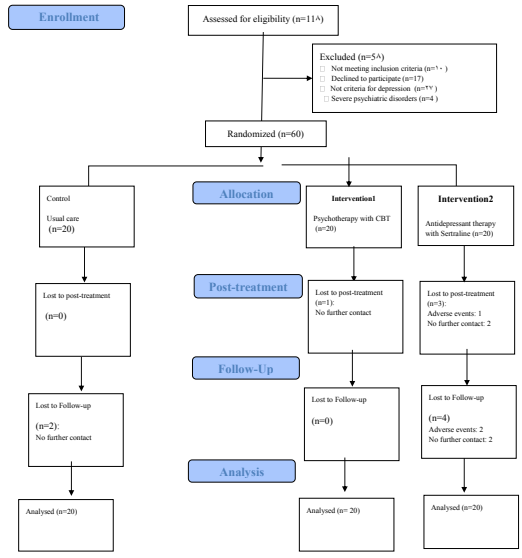

Fig.1: Flowchart of participants over the trial.

Table 1: Sessions outline of (FACBT)*

Sessions	Contents
1. Introduction of targets	Introduce program benefits, building empathy, Focused on setting strategies, problems related to infertility. Building a therapeutic alliance and obtaining information from the patient, identifying automatic thoughts about infertility, Home assignment: Coping diary. 30 minutes of daily attention to the five aspects of infertility stress.
2. Infertility stress	Reflection on, the last week and repetition. Emphasis on the therapeutic alliance. Training of A-B-C model of FCBT. Helping the patient to recognize that stressful thoughts about infertility teaching the use of the thought record. Home Assignment: Thought record (distinguish between rational and irrational thoughts). Attention to one stressful infertility experience.
3. Infertility stress related to the need for parenthood	Reflection on, the last week and repetition. Evoke Clinically Relevant Behaviors (CRB1s). Understanding thinking Errors. Dealing with automatic infertile thoughts in life and social concerns during a / the (please choose one of them) session. Home assignment: Seeking to fictional generalization and CRBs of infertility stress, especially the need for parenthood.
4. Infertility stress related to a child-free lifestyle	Reflection on, the last week and repetition. Self as control. Control as the infertility problem. Reinforcing CRB2s related to a child-free lifestyle. Attention to the acceptance of unchangeable events. Home assignment: Seeking to fictional generalization and CRBs** of infertility stress, especially the need for parenthood. Attention to the acceptance of a child-free lifestyle.
5. Infertility stress related to social concerns	Reflection on, the last week and repetition. Values clarification and commitment. Awareness in daily. Advancing CRB3s related to a child-free lifestyle. Dealing with automatic infertile thoughts in life related to social concerns. Home assignment: Seeking to fictional generalization and CRBs of infertility stress, especially social concerns.
6. Infertility stress related to the failure of ART	Reflection on, the last week and repetition. Dealing with difficult emotions about the failure of ART. Home assignment: Seeking to fictional generalization and CRBs of ART.
7. Infertility stress related to communication	Reflection on the last week and repetition. Dealing with difficult relationships. Home assignment: Careful attention to their relationship with their husband and others. Seeking to fictional generalization and CRBs of communication.
8. Self-compassion	Reflection on, the last week and repetition. Helping patients to love themselves. Home assignment: Attention to loving yourself with. Attention to detaching themselves from the infertility stress, the need for parenthood, rejection of a child-free lifestyle, social concerns, marital relationship problems, and marital problems. In addition, compassion for herself.
9. Calming down stressful thoughts related to infertility	Reflection on, the last week and repetition. Perspective Taking. Home assignment: Attention to the realization and nonjudgmental comprehension of the momentum of thoughts, especially about the ART failure, social concerns, marital concerns, and relationship concerns arising from unwanted thoughts about the five domains of infertility stress.
10. Relapse prevention	Helping the patient to develop a practice of her own, review of progress, insights, techniques, and the individual evaluation of the sessions. Reflection of the learned skills and final discussion.

***; The cognitive behavior therapy, enhancing with functional analytic therapy for women with infertility, **; The therapist used many techniques every session like, evoke CRBs, emotional validation, Increase the current effectiveness of certain stimuli infertility stimuli, or events as reinforcement, and positive reinforcement, and ART; Assisted reproductive technologies.**

Table 2: Demographic characteristics of the population study

Variables	CBT	Sertraline	Control	All patients
Age (Y)	32.7 ± 6.8	30.2 ± 4.9	32.2 ± 5.8	31.7 ± 5.9
Education (Y)				
<12	10 (50)	10 (50)	6.0 (30)	26 (43.3)
≥12	10 (50)	10 (50)	14 (70)	34 (46.7)
Job				
Employee	1.0 (5)	2.0 (10)	2.0 (10)	5.0 (8.3)
Unemployed	19 (95)	18 (90)	18 (90)	55 (81.7)
Number of abortion				
2	9.0 (45)	10 (50)	11 (55)	20 (33.3)
3	5.0 (25)	5.0 (25)	4.0 (20)	14 (23.3)
≥4	6.0 (30)	5.0 (25)	5.0 (25)	26 (43.4)
Duration of infertility (month)	69.6 ± 54.3	34.9 ± 8.2	60.6 ± 56.1	64.4 ± 49.0

Data are presented as mean ± SD or n (%). CBT; Cognitive behavior therapy.

Table 3: Within group effect sizes of the interventions from pre-treatment to post-treatment and follow-up in three groups of the trials

Outcomes	Description			Within group effect size pre-treat with post-treat	Within group effect size pre-treat with follow-treat
	Pre-treat	Post-treat	Fallow-up		
Depression					
CBT	23.1 ± 9.89	13.4 ± 12.2	16.1 ± 11.4	0.84 (0.30, 1.37)	0.54 (-0.01, 1.11)
Sertraline	23.4 ± 9.9	14.7 ± 10.2	22.9 ± 9.2	1.03 (0.53, 1.53)	0.08 (-0.21, 0.37)
Control	24.4 ± 8.1	24.2 ± 9.5	24.1 ± 9.5	0.02 (-0.30, 0.36)	0.04 (-0.29, 0.38)
Anxiety					
CBT	29.4 ± 7.3	45.4 ± 7.3	47.0 ± 6.7	0.42 (-0.15, 1.00)	0.25 (-0.35, 0.85)
Sertraline	51.5 ± 6.0	43.6 ± 5.6	46.9 ± 5.1	1.21 (0.58, 1.84)	0.83 (0.31, 1.35)
Control	47.5 ± 9.0	51.0 ± 8.5	50.2 ± 6.5	-0.38 (-0.86, 0.10)	-0.25 (-0.87, 0.36)
Infertility stress social concern					
CBT	34.9 ± 9.7	32.4 ± 9.8	30.6 ± 9.7	0.17 (-0.50, 0.85)	0.31 (-0.35, 0.97)
Sertraline	29.5 ± 8.3	28.2 ± 8.4	30.0 ± 6.9	0.16 (-0.23, 0.56)	-0.09 (-0.62, 0.43)
Control	30.0 ± 9.7	33.1 ± 11.5	35.8 ± 12.1	-0.23 (-0.73, 0.26)	-0.46 (-0.96, 0.04)
Sexual concern					
CBT	27.8 ± 7.6	24.4 ± 9.7	23.8 ± 9.6	0.28 (-0.32, 0.90)	0.28 (-0.42, 1.00)
Sertraline	24.2 ± 9.0	21.3 ± 8.8	23.7 ± 6.5	0.32 (-0.14, 0.79)	0.06 (-0.39, 0.53)
Control	22.9 ± 7.3	26.1 ± 8.9	26.0 ± 10.6	-0.40 (-0.84, 0.03)	-0.28(-0.82, 0.25)
Relationship concern					
CBT	35.9 ± 8.9	29.9 ± 9.3	30.5 ± 8.4	0.42 (-0.28, 1.13)	0.41 (-0.27, 1.10)
Sertraline	32.4 ± 10.0	29.4 ± 8.6	28.3 ± 6.8	0.36 (-0.05, 0.77)	0.52 (0.08, 0.95)
Control	30.2 ± 8.8	34.5 ± 8.7	34.5 ± 10.2	-0.50 (-0.96, -0.03)	-0.40 (-0.92, 0.12)
Reject of life without parenthood					
CBT	30.9 ± 9.8	26.9 ± 9.8	27.5 ± 9.0	0.35 (-0.16, 0.87)	0.30 (-0.23, 0.84)
Sertraline	23.3 ± 5.9	23.6 ± 4.8	28.6 ± 6.2	-0.06 (-0.43, 0.31)	-0.75 (-1.32, 0.18)
Control	31.1 ± 7.8	33.9 ± 7.3	32.2 ± 6.7	-0.63 (-0.96, -0.30)	0.94 (-1.34, -0.54)
Need for parenthood					
CBT	35.9 ± 12.4	29.5 ± 10.4	26.6 ± +9.7	0.58 (0.11, 1.05)	-0.03 (-0.69, 0.62)
Sertraline	38.7 ± 9.8	35.6 ± 10.1	39.2 ± 9.7	0.36 (-0.03, 0.77)	-0.05 (-0.40, 0.28)
Control	39.5 ± 9.5	39.3 ± 11.3	44.0 ± 10.3	0.02 (-0.31, 0.37)	-0.65 (-1.02, -0.28)
Total score					
CBT	165.6 ± 36.4	143.1 ± 34.3	149.1 ± 31.9	0.42 (-0.24, -1.10)	0.30 (-0.39, -1.01)
Sertraline	148.3 ± 34.6	138.2 ± 33.5	150.12 ± 9.0	0.34 (-0.05, 0.74)	-0.06 (-0.47, 0.35)
Control	154.1 ± 23.2	163.3 ± 42.7	175.6 ± 40.0	-0.25 (-0.70, 0.19)	-0.61 (-1.10,- 0.11)

Data are presented as mean ± SD or g (95% CI). Rang scores: Depression, 0-63; State anxiety, 20-80; Trait anxiety, 20-80; Social concern (1-60), sexual concern (1-48), relationship concern (1-60), rejection of life without child (1-48), need for parenthood (1-60), total scores of infertility stress (46-276). CBT; Cognitive behavioral therapy, *; Linear mixed models with random intercept time, treatment group, and time-group interaction as fix factors were used to estimate each outcome measure in three groups of the trial, P<0.05. The effect sizes (Hedges' g) were defined as small (g=0.20), medium (g=0.50), and large (g=0.80).

Treatment outcomes

Depression

In the CBT group, the score of depression, decreased more significantly in the post-trial than pre-trial with a large effect size [g (95% CI)=0.84 (0.30, 1.37)] and at follow-up over pre-trial with a moderate effect size [g (95% CI)= 0.54 (0.14, 1.11)]. In the sertraline group, the depression symptoms diminished more significantly at post-trial than at pre-trial with a large effect size [g (95% CI)=1.03 (0.53, 1.53)]. In the control group, the depression symptoms did not change significantly from pre-trial to post-trial and also, in the follow-up (Table 3).

There were significant group- time interactions for the severity of depression symptoms according to the BDI-II [F (4, 196.08)=4.96, P=0 .001)]. CBT decreased the depression symptoms more significantly, while the sertraline group showed a moderate effect size at the post-trial [g (95% CI)=0.11(-0.03, -0.50)] and large effect size at follow-up [g (95% CI)=-1.60 (-1.31, -0.03)]. The depression, diminished more significantly in the CBT group than in the control group with a large effect size at the post-trial [g (95% CI)=-1.00(-1.66, -0.27)] and follow-up [g (95% CI)=0.78 (-1.42, -0.11)]. Also, in the sertraline group, we observed a significant decrease in the depression symptoms in comparison with the control group, with a large effect size at the post-trial [g (95% CI)= -0.97 (-1.63, -0.32)], but not at follow-up (Table 4).

In the CBT and control groups, anxiety scores did not change significantly at post-trial than pre-trial and also, at follow-up in comparison with pre-trial. In the sertraline group, the score of anxiety dropped more significantly at post-trial than at pre-trial with a large effect size [g (95% CI)=1.21 (0.48, 1.84)] and at follow-up in comparison with pre-trial with a large effect size [g (95% CI)=0.83 (0.31, 1.35)].

There were significant group-time interactions among three groups for the severity of anxiety symptoms, according to state-anxiety [F (4, 174.33)=5.20, P=0 .001)]. There were no significant differences between the CBT group and the sertraline group in reducing the anxiety at post-trial and at follow-up. The scores of state-anxiety did not change significantly in the CBT group over the control group at post-trial and follow-up. Sertraline group lowered the scores of state-anxiety more significantly than the control group did with a large effect size of the post-trial [g (95% CI)=-1.04 (-1.70, -0.38)], but not follow-up.

Infertility stress

In the CBT group, the total score of infertility stress diminished more considerably at post-trial with a moderate effect size [g (95% CI)=0.42 (-0.24, -1.10)] and at follow-up with a moderate effect size [g (95% CI)= 0.32 (-0.39, -1.01)]. Of five subscales of FPI, CBT group showed the 'need to parenthood concerns' scale more considerably at post-trial with a moderate effect size [g (95% CI)=0.58 (0.11, 1.05)] and at follow-up in comparison with pre-trial with a moderate effect size [g (95% CI)=0.30 (-0.39, -1.01)]. The CBT group showed a more significant decrease in the total scores of infertility stress in comparison with the sertraline group, with a large, small size at follow-up [g (95% CI)=-0.03 (-0.65, -0.58)].

In the sertraline group, the total score of infertility stress did not change significantly at post-trial and follow-up. Of five subscales of FPI, only the sertraline group showed a decrease in scores of 'marital relationship concerns' more considerably in the post-trial with a moderate effect size [g (95% CI)=0.52 (0.08, 0.95)].

In the control group, the total score of infertility stress and the social concerns did not change considerably in the post-trial, but those scores increased significantly more at follow-up with a large effect size [g (95% CI)=0.61 (-1.10, -0.11). Also, the concerns about 'rejection of parenthood increased significantly in post-trial with a large effect size [g (95% CI)=-0.63(-0.96, -0.03)] and follow-up [g (95% CI)=-0.40 (-0.92, -0.12)]. Also, the score of 'concerns about the need of parenthood' increased significantly in the follow-up period than at pre-trial with a large effect size [g (95% CI)=-0.65 (-1.34, -0.54)].

Table 4: Between effect sizes of the interventions from pre-treatment to post-treatment and follow-up in three groups of the trials

Outcomes	CBT and sertraline*		CBT and control**		Sertraline and control*	
Depression	**Post**	**Follow up**	**Post**	**Follow up**	**Post**	**Follow up**
Anxiety	-0.11 (-0.73, -0.50)*	-0.67 (-1.31, -0.03)*	-1.00 (-1.66, -0.27)*	-0.78 (-1.42, -0.11)*	-0.97 (-1.63, -0.32)*	-0.13 (-0.75, 0.48)
Infertility stress	0.27 (-0.34, 0.90)*	0.02 (-0.59, 0.64)	-0.72 (-1.36, 0.11)*	-0.50 (-1.13, 0.18)*	-1.04 (-1.70, -0.38)*	-0.59 (-1.22, 0.04)*
Social concern	0.46 (-0.16, 1.09)	0.03 (-0.58, 0.65)	-0.06 (-0.68, 0.53)	-0.48 (-1.11, -0.10)	-0.49 (-1.12, 0.13)	-0.57 (-1.20, 0.05)
Sexual concern	0.34 (-0.27, 0.96)	0.01 (-0.60, 0.63)	-0.18 (-0.81, 0.65)	-0.22 (-0.84, 0.11)	-0.55 (-1.18, 0.07)	-0.27 (-0.89, 0.35)
Relationship	0.05 (-0.56, 0.67)	0.29 (-0.32, 0.91)	-0.52 (-1.15, -0.08)	-0.44 (-1.07, 0.12)	-0.59 (-1.22, 0.03)	-0.73 (-1.38, -0.09)*
Reject of parenthood	0.44 (-0.18, 1.06)	-0.13 (-0.75, 0.48)	-0.82 (-1.47, 0.09)	-0.99 (-1.64, -0.10)	-1.70 (-2.42, -0.98)*	-1.05 (-1.71, -0.39)
Need to parenthood	-0.61 (-1.24, 0.02)	-0.27 (-0.89, 0.34)	-0.92 (-1.58, -0.34)	-0.75 (-1.39, -0.14)	-0.35 (-0.98, 0.26)	-0.49 (-1.11, 0.13)*
Total scores	0.14 (-0.47, 0.77)	-0.03 (-0.65, -0.58)*	-0.53 (-1.16, -0.18)	-0.74 (-1.38, -0.33)	-0.67 (-1.30, -0.03)*	-0.74 (-1.38, -0.10)*

Data are presented as g (95% CI). CI; Confidence interval, CBT; Cognitive behavioral therapy, **; Linear mixed models with random intercept time, treatment group, and time-group interaction as fix factors were used to estimate each outcome measure in three groups of the trial, *; P<0.05. The effect sizes (Hedges' g) were defined as small (g=0.20), medium (g=0.50), and large (g=0.80).

There were significant group-time interactions between three groups for the total score of infertility stress, according to FPI [F (4, 2097.24)=2.97, P=0.022)]. Also, there were significant group-time interactions for two subscales of FPI, including marital concern [F (4, 189.6)=3.05, P=0 .008)] and rejection of parenthood [F (4, 127.23)=4.15, P=0 .004)]. The CBT group had a reduction at total scores of infertility stress more considerable than the sertraline group, with a large, small size at follow up [g (95% CI)=-0.03 (-0.65, -0.58)]. The CBT group had a reduction in the infertility stress scores more than the control group, with a large effect size in the post-trial [g (95% CI)=-0.53 (-1.16, -0.18)] and follow-up [g (95% CI)=-0.74 (-1.38, -0.33)]. Also, sertraline group showed less infertility stress than the control group, with a large effect size at the post-trial [g (95% CI)=-0.67 (-1.30, -0.03)] and follow-up [g (95% CI)=-0.74 (-1.38, -0.10)]. The CBT group had a decrease at scores of "the need to parenthood of infertility stress" more than the control group, with a large effect size at the post-trial [g (95% CI)=-0.92 (-1.58, -0.34)] and follow-up [g (95% CI)=-0.75 (-1.39, -0.14)]. Also, CBT group had a reduction in scores of 'rejection of parenthood' more than the control group did at follow-up with a large effect size [g (95% CI)=-0.99 (-1.64, -0.10)]. The sertraline group also had a reduction at scores of the following subscales of infertility of stress more than control did; social concerns at post-trial with a moderate effect size [g (95% CI)=-0.49 (-1.12, -0.13)], marital relationship concerns at follow-up with a large effect size [g (95% CI)=-0.73 (-1.38, -0.09)], and rejection of parenthood with a moderately small size of post-trial [g (95% CI)=-1.70 (-2.42, -0.98)] and follow-up [g (95% CI)=-0.49 (-1.11, -0.13)].

Secondary outcomes

Treatment compliance

Dropout rates were 5% (19/20) in the CBT group, 35% (13/20) in the sertraline arm, and 10% (18/20) in the usual care group. Out of 20 women of the CBT group, 19 persons provided post-trial (95%) and follow-up data (95%). 17 women of the sertraline group, (17/20, 85%) provided post-trial and 13 persons (65%) provided follow-up data. Women in the CBT group were more likely than those in the sertraline group to complete trial at the follow-up assessments [$\chi 2(1)=5.625$, P=0.02; OR (95% CI)=1.46 (1.04, 2.04)]. The CBT group (n=15 /20) attended 8.10 ± 1.83 sessions (mean ± SD) from 10 sessions (with the psychologist), (75% compliance). The mean number of sertraline sessions contacted with the psychiatrists was 2.60 (SD 1.23) from 5 sessions of formal contact with psychiatric. Also, 11 women of the sertraline group contacted with psychiatrist 3 to 5 sessions of formal contract for the treatment (55% compliance).

Treatment satisfaction

The mean score treatment satisfaction of the participations in the CBT group was very significantly higher (4.26 ± 0.99, rated; 1-5) than the scores of those treatment satisfaction with sertraline group (2.12 ± 1.08, t=6.081, P<0.001).

Discussion

Here, we compared the efficacy of psychotherapy with pharmacotherapy in improving depression, anxiety, and pregnancy stress of depressed infertile women with RPL. We found that both CBT and sertraline led to moderate to large improvements in the scores of depression and infertility stress in these women. Regarding depression amelioration, both CBT and sertraline were superior to the control group, and CBT was superior to sertraline, with a moderate to large effect size of post-trial and follow-up.

This study has been the first RCT to compare the effect of CBT with sertraline in depressed infertile women with RLP history, therefore, we could not find any research to use sertraline in the treatment of depression in the RPL women. Although, there was an RCT that had compared the effect of CBT vs. sertraline in the diabetic patients who suffered from major depression. They reported that both CBT and sertraline improved the depression in their patients, with a superiority for sertraline (32).

In line with our results, Nakano et al. (14) investigated the effect of individual CBT on the 14 patients with RLP and depression/anxiety. They observed that CBT was useful in the improving the scores of depressions based on the BDI-II measurement. Although in both studies, CBT reduced the depression of women, there have been differences between our study and Nakano' study. Respectively, these differences include: population (the infertile women of vs. non infertile women), the number of groups in the study (three groups, including CBT, sertraline, and control vs. one group, only CBT), and the design of the study (RCT vs. interventional study with pretest-posttest design).

The important question of these results is that how the efficacy of CBT in the treatment of depression, persisted until 3-month follows-up against sertraline. There are some assumptions. First, in psychotherapies such as CBT, the thoughts can be altered, which may be persisted for a long time or even forever. Secondly, the CBT group had more treatment adherence in comparison with the sertraline group. The attendance and cooperation in the treatment of CBT group were greater than the sertraline group. Also, participants in the CBT group also, received group psychotherapy with more benefits than individual therapy such as giving valuable support from the group, sharing feelings and experiences in the group, and receiving corrected feedback. Finally, patients who received sertraline had worries regarding the effect of sertraline on their fertility or their future children.

In the present study, sertraline, showed a reduce score of anxiety more significantly than the control group, with a large effect size at post-trial, but not at follow-up. There were no significant differences between CBT

and sertraline in reducing the anxiety at post-trial and at follow-up. Inconsistent with our results, a study reported that CBT reduced the anxiety of depressed women with RPL (14). Also, results of a systematic review reported that psychological support and interventions may reduce levels of stress, anxiety or depression on subsequent pregnancy of women with a miscarriage history (33). Our previous RCTs also revealed that CBT was an efficient approach in reducing the anxiety in infertile women (18, 34).

It is important to explain why CBT did not improve the anxiety of infertile women. It may be related to the treatment approach. First, we used a model of CBT enhanced with FACBT which emphasized infertility-specific stress, rather than general anxiety. Secondly, the focuses of therapy were treatment of depression, not anxiety symptoms. Finally, the practices for anxiety improvement were minor. Wenzel (35) suggested that interventional strategies such as cognitive restructuring, behavioral activation and mindfulness are essential in the patients with RPL. Focus on improving anxiety along with the depression is recommended for future psychotherapies research.

In the present study, CBT reduced the total scores of infertility stress more considerably than sertraline, with a large, small size at follow-up, but not at post-trial. Both CBT and sertraline were superior to the control group in mitigating infertility stress. We propose two assumptions. First, considering the mean value of infertility stress of depressed the infertile women at the baseline, we found that the mean level of infertility stress in the CBT group was higher than the sertraline group (165 ± 36.4 vs. 148.3 ± 34.3, respectively) in pre-treatment. Although, both CBT and sertraline reduced the total score of infertility stress at the post-treatment (138 ± 33.5 vs. 149.1 ± 34.3, respectively), this reduction was not considerable at post-trial. When the infertility stress mitigation in the CBT group continued to the follow-up, the different effect of CBT and sertraline would be significant. Secondly, as the effectiveness of CBT was required for practice of skills, reducing symptoms of the infertility stress in CBT lasted longer compared with sertraline.

Note that in this study, both CBT and sertraline changed only in the some subscales of infertility stress. For explaining these effects, we propose three reasons. First, considering the mean scores and range of scores at baseline, it is found that the mean of these two subscales was higher than that of the three others infertility subscales from the beginning. Secondly, the main effect of CBT and sertraline in mitigating infertility stress, especially the total score of the FPI, was on reducing "rejection of life without parenthood" and "need to parenthood". Third, these subscales are very important in the infertile women with RPL history in comparison with the control group. And, two subscales of FPI "rejection of life without parenthood" and "need to parenthood" increased in post-trial and follow-up.

These findings have particularly important clinical implications for gynecologists, psychiatrists, and psychologist. This study suggests that both CBT and sertraline are sufficient in the reducing depression and infertility stress of infertile women with RPL, history with a significant advantage favoring CBT. On the other hand, sertraline was superior to CBT in mitigating the anxiety score. The CBT group showed greeter adherence and satisfaction with the treatment than sertraline. Further study is required to investigate how to increase the adherence and satisfaction with pharmacotherapy in the infertile women with RPL.

While these findings are promising, there are some limitations to be noted. First, the disproportional number of dropouts from the CBT group and sertraline group was not addressed well. The dropouts of the pharmacotherapy were high. Of the six participants who discontinued taking sertraline, three patients explained that they experienced side effects such as agitation, nausea, and vomiting. Also, three other patients did not respond to our contacts with phone or social networks such as WhatsApp. Further research is required to assess the obstacles against infertile women with RPL history that taking anti-depressants medicine. Moreover, our results were provided from one infertility clinic of a small city. A multicenter study is a better choice for further studies. In addition, further research is needed to evaluate other psychotherapy interventions and other antidepressant effect on the anxiety and depression in this patients. Confirming our findings, require to test potential moderators influencing psychotherapy or sertraline response, and address an acceptance of therapy model.

Conclusion

This study provided preliminary support for the efficacy of CBT and sertraline therapy for infertile women with RPL history and offered a range of further research opportunities in this field. Future research is also necessary to demonstrate whether routine CBT/pharmacotherapy adjoined with treatments of ART would prevent the negative psychological consequences in these patients. Assessing whether adding CBT or sertraline to therapies is cost-effective for the treatment of depressed infertile women with RPL is also another research area.

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Authors' Contributions

M.F.; Participated in study design, drafted the manuscript. F.Kh.; Was responsible for overall supervision, revised the drafted manuscript. Z.B., S.E.; Conducted project managing. S.Kh.; Contributed extensively in interpretation

of the data and the conclusion. Z.T.; Contributed to data gathering. All authors contributed to the drafting of this manuscript and approved the final.

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