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ORIGINAL ARTICLE

Prophylactic SSRI treatment for women suffering from mood and anxiety symptoms undergoing in vitro fertilization—a prospective placebo-controlled study

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Abstract

To explore the mood protective effect of prophylactic SSRI treatment on women undergoing IVF suffering from moderate affective and anxiety symptoms. In a randomized double blind, placebo-controlled, parallel design study, 41 women diagnosed with an Adjustment Disorder, who were undergoing IVF treatments, were randomized into two groups; a study group ($n = 22$) administered escitalopram 10 mg/day, and a control group ($n = 19$) administered placebo for a total of 8 weeks before and during the IVF treatment cycle. Patients were assessed at the onset of drug treatment and at embryo transfer. The main outcome measure was the difference in mean score severity rating of depression and anxiety symptoms on the CES-D and Zung questionnaires between groups at the time of embryo transfer. Secondary outcome measures included the MHI rating subscales addressing aspects of psychological distress and coping. At the day of embryo transfer (6 weeks of drug treatment), the CES-D average score for the treatment group was 6.40 (6.71) and 27.47 (4.29) on the Zung Self-Rating Anxiety Scale, while the placebo group scored an average of 15.83 (8.69) and 33.17 (6.95) receptively. These findings were significant ($p = .004$, $p = .015$ receptively) and were endorsed by the scoring on the MHI questionnaire subscales. Short-term treatment with SSRI may serve as a prophylactic treatment against the perpetuation and possible worsening of depressive and anxiety symptoms in women undergoing IVF treatments. Further studies concerning pharmacological interventions in larger samples and studies addressing screening for psychological stress indicators in this population are warranted.

Keywords Depression · Anxiety · Antidepressant therapy · SSRI · In vitro fertilization

Introduction

In vitro fertilization (IVF), a type of assisted reproductive technology (ART), is a common procedure in couples and women with fertility problems. The usage of ART has doubled over the past decade, and today, approximately 1.6% of all infants born in the USA every year are conceived using ART. In Israel, more than 35,000 IVF cycles are performed per year.

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Over the past years, a number of studies have been published concerning the association between psychiatric disorders and reproductive failure (Klonoff-Cohen et al. 2001). One suggested link is that psychological factors serve as risk factors for subsequent infertility. Klonoff-Cohen et al. (2001) found that baseline (acute and chronic) stress negatively affects biologic end points (i.e., number of oocytes retrieved and fertilized), as well as biochemical pregnancy, live birth delivery, birth weight, and multiple gestations. To date, supporting evidence for this association is meager, and studies are contradictory (Anderheim et al. 2005; Lintsen et al. 2009). Another line of research investigated the claim that a diagnosis of infertility and the treatments involved cause subsequent psychological distress (Cwikel et al. 2004; Bloch et al. 2011). A bi-directional association between infertility and psychosocial distress was proposed as well, so both might be affecting concurrently (Cwikel et al. 2004; Thiering et al. 1993).

Several studies addressed the issue of depressive and anxiety symptoms among women undergoing IVF. Domar et al. (1992) found that among infertile women, 37% had significant depressive symptoms on the Beck Depression Inventory (BDI), twice as common as in a control group. Moreover, at the onset of IVF treatment, 54% of infertile women were found to be mildly depressed and 19.4% to have moderate to severe depressive symptoms (Demyttenaere et al. 1998). Other studies found that prior to IVF treatment, 11.6% and 33% of the treated women reported significant depressive symptoms according to the BDI and General Health Questionnaire, respectively, while the frequency was increased to 25.4% and 43%, respectively, following failed IVF. Anxiety symptoms in infertile women were encountered in 10.6% of women prior to IVF treatments and in 14.2% of women after the treatments (Newton et al. 1990; Lok et al. 2002). In a study performed in our department in collaboration with the Infertility Unit in the Tel Aviv Sourasky Medical Center, 108 women undergoing IVF treatments were investigated using the Structured Clinical Interview for DSM Disorders (SCID). It was found that women suffering from an axis I psychiatric disorder (Frances et al. 1994) in the past or the present developed significantly more depressive and anxiety symptoms during certain stages of the treatment cycle compared to women who did not suffer from a psychiatric disorder (Zaig et al. 2013). Sbaragli et al. (2008) found that a high percentage of infertile patients developed an adjustment disorder (40%) preceding any medical intervention. Prospective studies have also demonstrated that pretreatment levels of depression and anxiety symptoms are predictive of depressive symptomatology after treatments (Khademi et al. 2005). Further, and most importantly, it was found that the majority of subjects with a psychiatric disorder were undiagnosed, and only a small proportion of those identified received ongoing treatment, despite the obvious importance of reaching a rapid remission in these women. One possible explanation as to why depression is usually unrecognized in the infertility setting could be that infertile couples are reluctant to report depressive symptoms to the IVF team (Volgsten et al. 2008), and also, that in most IVF units patients are not subjected to routine psychiatric questioning.

A number of studies addressed the issue of the effects of psychotherapeutic interventions on various outcomes in infertile women and couples (Campagne 2006). Frederiksen et al. (2015) suggest that psychosocial interventions, in particular Cognitive Behavioral Therapy (CBT) and mind/body interventions, are beneficial for reducing distress and for improving pregnancy outcomes of ART. However, a Cochrane Database Systematic review that was published in 2016 concluded that the effects of psychological and educational interventions on mental health including distress and live birth or ongoing pregnancy rates are uncertain due to the very low quality of the evidence (Verkuijlen et al. 2016). Publications concerning pharmacologic interventions for mood or anxiety symptoms for IVF patients are almost nonexistent and are inconclusive (Serafini et al. 2009).

In the current randomized double blind, placebo-controlled study, we examined the effect of a prophylactic selective serotonin reuptake inhibitor (SSRI) treatment on women undergoing IVF treatment who were suffering from an adjustment disorder with moderate affective and anxiety symptoms. We hypothesized that even in this moderately symptomatic population, a short-term treatment with an SSRI, prior to the launching of an IVF treatment cycle, will result in the prevention of worsening of affective and anxiety symptoms compared to placebo at the point of embryo transfer.

Methods

Eligibility criteria

Participants were women aged 18–45 recruited from the Tel Aviv Sourasky Medical Center IVF program, between August 2010 and October 2015. The accepted indications for the fertility treatments were female factor, male factor, both, or unexplained infertility. Patients were eligible if they met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) SCID diagnosis of an adjustment disorder. Exclusion criteria were as follows: an axis I DSM-IV diagnosis other than an adjustment or anxiety disorder; suicidal ideation; current treatment with antidepressant medication; physical illness explaining affective or anxiety symptoms; substance abuse and dependence; past severe side effects to SSRIs; and failed IVF (four trials of good quality embryo reinstatement without achieving pregnancy).

Study procedure

Participants underwent a baseline examination including a comprehensive psychiatric interview, medical history, and the following self-report questionnaires: a demographic questionnaire, the Zung Self-Rating Anxiety Scale (Zung 1971), Center for Epidemiologic Studies Depression (CES-D) Scale (Radloff 1977), the Quality of life questionnaire–Mental Health Inventory (MHI) (Veit and Ware 1983), and a Side effects scale.

Informed consent was obtained from all participants included in the study. Women meeting the study criteria were randomized into two groups. Each group was administered 5 mg of escitalopram or placebo for a week, and then 10 mg for a total of at least 30 days before the first day of the menstrual cycle, after which the IVF treatment commenced. The rational for the time lag period prior to the initiation of the IVF course was to achieve the expected SSRI beneficial effect and

create a protective effect against intensification of the symptoms during the IVF course. Drug treatment continued throughout the IVF cycle and was terminated as soon as positive blood βHCG value was received (about 4 weeks after menses). Thus, total drug treatment period was 8 weeks. Patients were assessed by a trained psychiatrist blinded to group assignment, twice. The first assessment was carried out 30 days before the first day of IVF cycle and encompassed a full psychiatric assessment, recruitment, randomization, and beginning of pharmacological treatment. The second assessment was performed on the day of embryo transfer (app. 6 weeks after initiation of drug treatment), and encompassed a psychiatric follow-up. Findings regarding changes in anxiety and stress levels across the IVF cycle are inconclusive. While some studies show that anxiety and depression levels decline at the time of embryo transfer (Merari et al. 1992), other studies have shown that anxiety and stress did not significantly change across the IVF cycle, or even rose significantly adjacent to embryo transfer (Mahajan et al. 2010; Turner et al. 2013; Yong et al. 2000). We set the second assessment to the day of embryo transfer since we assumed this point to reflect significant stress levels in the IVF cycle. The date of serum βHCG was not chosen as the final assessment point since some of the patients went into menstruation or preformed a pregnancy urine test at home prior to completing the final psychiatric assessment rendering the population heterogeneous.

Data analysis

The main outcome measure for this study was defined as the between-group difference in mean score severity rating of depression and anxiety symptoms on the CES-D and Zung questionnaires at the time of embryo transfer. Secondary outcome measures included the MHI rating subscales addressing aspects of psychological distress and coping. As the objective of the study was to prevent significant depression during the treatment cycle, the time point used in the analysis was the second assessment performed during embryo transfer. Data analysis was performed using the SPSS software package (version 24). Means, standard deviations, and frequencies were used as descriptive statistics. Comparisons between groups were made using χ^2 tests for nominally scaled variables, and independent t tests for continuous scaled variables. All significance tests were two-sided and performed at a required significance level of 0.05.

Results

Ninety-four women were assessed for the study, of whom 53 were found unsuitable for the protocol. Forty-one women met the inclusion criteria to participate in the study and were randomized into a treatment group ($n = 22$) and a control group ($N = 19$). In the treatment group, three women dropped out due to drug side effects, one stopped medications, and two women did not reach the stage of fertilization. In the control group, one woman stopped the protocol due to a surgical procedure, one stopped medications, one dropped out for an unknown reason, and three women did not reach the stage of fertilization. Two additional women (one on each group) were excluded from the data analysis since they were recruited during the 2014 Israel–Gaza conflict which distorted the findings due to an overall rise in stress levels. Overall, 27 women were included in the data analysis (treatment group $n = 15$, control group $n = 12$). The data described above is shown in Fig. 1.

Sample characteristics

Descriptive information pertaining to the sociodemographic characteristics of women in the full sample used for analysis ($N = 27$) is reported in Table 1. Fertility and psychological characteristics are reported in Table 2. No significant differences between the two groups (treatment vs. placebo) were observed at time of enrollment. Psychiatric measures were compared between the two study groups at baseline to verify that there were no significant differences between them. Indeed, no such difference was found between the groups either in levels of anxiety as measured by the Zung questionnaire, level of depression as measured by the CES-D questionnaire, or the global mental health index measured by the Mental Health Inventory (MHI) at baseline.

Effect of treatment on mental state at the day of embryo transfer

At T_2, the day of embryo transfer, women who were treated with escitalopram (treatment group) scored 6.40 (6.71) in average on the CES-D and 27.47 (4.29) on the Zung Self-Rating Anxiety Scale, while women treated with placebo (control group) scored an average of 15.83 (8.69) on the CES-D and 33.17 (6.95) on the Zung Self-Rating Anxiety Scale. These findings demonstrate significantly lower subjective levels of depression and anxiety among women in the treatment group vs. women treated with placebo after approximately 6 weeks of drug treatment ($t(25) = 3.18$, $p = .004$; $t(25) = 2.62$, $p = .015$, respectively) as presented in Tables 3 and 4 and Fig. 2. These findings were further endorsed by the scoring on the MHI questionnaire subscales which showed a significant advantage to active treatment as can be appreciated from Table 3.

Discussion

The question addressed in this study was whether treatment with a short course of the SSRI escitalopram is beneficial in

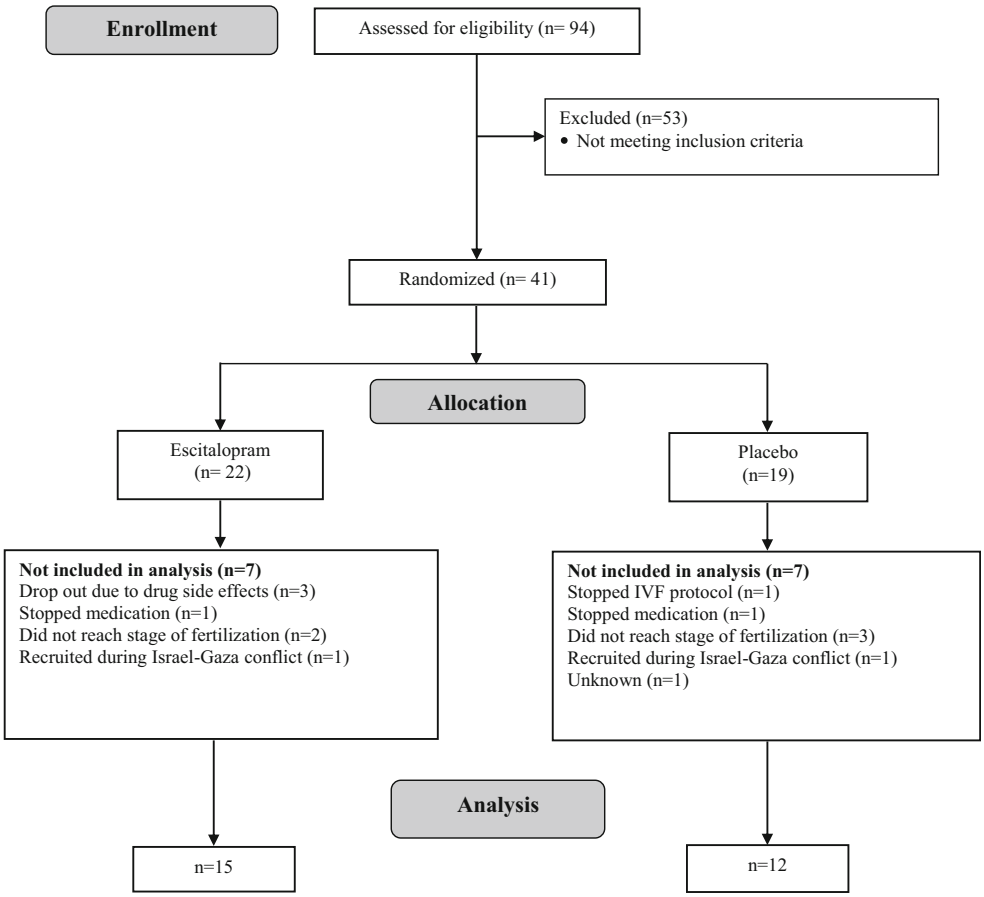

Fig. 1 Patient flowchart

protecting women against depressive and anxiety symptoms while undergoing IVF. Our results show that the study group, treated by escitalopram for a period of 6 weeks (about 4 weeks prior to IVF course initiation and 2 weeks up to embryo transfer), demonstrated significantly lower subjective levels of depression and anxiety than women treated with placebo, as well as a significant advantage in the majority of subscales of the MHI questionnaire, at the day of embryo transfer. While the abundance of depressive and anxiety symptoms among females undergoing IVF is a well-established fact, data regarding pharmacologic treatment aimed at preventing these disabling symptoms are scarce. In their study, Smeenk et al. (2001) proposed that a relationship exists between psychological variables and the probability of becoming pregnant after IVF treatment, while controlling other factors. Other studies show that chronic stress not only affects biological end-points, i.e., the number of oocytes retrieved and fertilized, but also affects pregnancy, live birth delivery, birth weight, and multiple gestations (Klonoff-Cohen et al. 2001). Various studies found that there is a relationship between psychological distress and IVF dropout rates and success (Domar 2004). There is also some information suggesting that counseling throughout IVF cycles lowers anxiety and depression scores in addition to improving pregnancy rates (Terzioglu 2001). Although counseling services are much needed, they are not always accessible or may be costly. On the other hand, research has shown that only a minority of fertility patients participate in counseling sessions, even when they are offered for free (Domar 2004). In view of this data, the pharmacological option is a sensible one.

The population of our study included women who were diagnosed as suffering from an adjustment disorder and not from a major mood or anxiety disorder. At the time of recruitment, their mean CES-D scores were 19.60 (± 9.70) and 24.33 (± 9.58) for the treatment group and the placebo group, respectively (cutoff point 16, score range 0–60) and 35.93 (± 7.28) and 36.17 (± 8.40) on the Zung anxiety scale, respectively (cutoff point 45, score range 20–80). These results represent a rather healthy and functioning non-psychiatric population. Since participants were diagnosed as suffering from an adjustment disorder, the reactive symptoms may cause disability and a vast amount of subjective distress. Despite the relatively low symptom severity and the small number of participants, we were able to show that at the day of embryo transfer, about 6 weeks after onset of pharmacological intervention, women treated with escitalopram demonstrated significantly lower subjective levels of depression and anxiety than women treated with placebo on both the CES-D and Zung Scales. Further, the majority of subscales of the MHI Questioner differed significantly between the two groups. These findings, to our opinion, demonstrate the protective effect a short

Table 1 Demographic characteristics of the sample ($N = 27$)

	Treatment group ($n = 15$)	Placebo group ($n = 12$)	Statistical test	p
Age, mean (SD), years	44.60 (3.25)	41.83 (4.28)	$t(25) = -1.91$	$p = .068$
Country of birth, *n* (%)			$\chi^2(4, N = 27) = 3.76$	$p = .44$
Israel	12 (80)	11 (91.7)		
Other	3 (20)	1 (8.3)		
Marital status, *n* (%)			$\chi^2(3, N = 27) = 1.71$	$p = .64$
Married	5 (33.33)	5 (41.7)		
Single	7 (46.67)	4 (33.3)		
Divorced	1 (6.67)	0 (0)		
Unmarried with a partner	2 (13.33)	3 (25.0)		
Nationality, *n* (%)				
Jewish	15 (100)	12 (100)		
Religiosity, *n* (%)			$\chi^2(2, N = 27) = .86$	$p = .65$
National-religious	1 (6.67)	0 (0)		
Traditional	2 (13.33)	2 (16.7)		
Secular	12 (80)	10 (83.3)		
Educational level, *n* (%)			$\chi^2(4, N = 27) = 2.97$	$p = .56$
No high school diploma	1 (6.67)	1 (8.3)		
High school graduate	1 (6.67)	1 (8.3)		
Further education	2 (13.33)	3 (25)		
Undergraduate degree	3 (20)	0 (0)		
Graduate degree	8 (53.33)	7 (58.3)		
Employment, *n* (%)			*	$p = .61$
Employed	13 (86.67)	10 (83.3)		
Unemployed	2 (13.33)	2 (16.7)		
Income, *n* (%)			$\chi^2(3, N = 27) = 4.21$	$p = .24$
Above average	6 (40)	5 (41.7)		
Average	4 (26.67)	6 (50)		
Below average	4 (26.7)	0 (0)		

No significant differences between treatment group and placebo group were observed

χ^2 chi-squared test, *t* independent two group Student's *t* test, *SD* standard deviation

*Fisher exact test

treatment course of SSRI may have over this population in which depressive and anxiety symptoms are so abundant.

Our findings emphasize two key points: The first point focuses on pharmacologic treatment with an SSRI for patients who suffer from moderate mood or anxiety symptoms. As we demonstrated in our study, even a short course of SSRI treatment may significantly attenuate the depressive and anxiety symptoms in treated women, as well as worsening of psychological distress. The reduction in mental distress may possibly have a positive effect on IVF outcomes and may allow these patients to see the fertility treatment through. In our design, SSRI treatment was stopped upon receiving a positive pregnancy test in order to refrain from any potential teratogenic impact of medication on the developing fetus. Since participants were suffering from mild to moderate symptoms which probably evolved in reaction to fertility difficulties and treatments, and since medication were given as a protective measure against worsening of symptoms, we concluded it would be safe to stop the medication once pregnancy was established without expecting mental health deterioration.

The second point concerns psychiatric screening of candidates for fertility treatments. In many countries, there is no mandatory psychiatric screening for fertility patients. This situation may lead to overlooking the patient's mental health since the majority of patients present with mild symptoms, or an ongoing adjustment disorder, rather than a full blown affective or anxiety disorder. Further, patients may abstain from confiding in the fertility practitioners about their mental state in fear of stigma and concerns about being denied the possibility of fertility treatment. An inherent methodical psychiatric screening may identify those patients who are symptomatic and in turn offer them accessible treatment which may improve their

Table 2 Fertility and psychological characteristics of the sample on the enrollment day ($N = 27$)

	Treatment group ($n = 15$)	Placebo group ($n = 12$)	Statistical test	p
Number of spontaneous pregnancies in the past	.73 (1.1)	.7 (1.3)	$t(25) = .04$	$p = .97$
Number of pregnancies resulting from treatments	.07 (.26)	.25 (.45)	$t(25) = 1.25$	$p = .23$
Number of spontaneous births in the past	.13 (.35)	.25 (.45)	$t(25) = .75$	$p = .46$
Number of births resulting from treatments	.07 (.26)	.08 (.29)	$t(25) = .16$	$p = .88$
Number of years since fertility treatment began[a]	.90 (.81)	1.01 (.53)	$t(23) = .36$	$p = .72$
Suffers from medical problems, *n* (%)	6 (40)	4 (33.3)	*	$p = .52$
Previously suffered from depression, *n* (%)	1 (8.3)	2 (14.29)	*	$p = .70$
Suffered from anxiety (past or present), *n* (%)	3 (20)	2 (16.7)	*	$p = .61$
Has seen a psychiatrist or a psychologist, *n* (%)	9 (60%)	7 (58.3%)	*	$p = .62$
Past psychiatric diagnosis, *n* (%)	0 (0%)	0 (0%)	*	$p = .48$
Medication period length up to embryo transfer, days	46.40 (13.74)	51.83 (17.48)	$t(25) = .90$	$p = .37$
Depression at enrollment—CES-D	19.60 (9.70)	24.33 (9.58)	$t(25) = 1.27$	$p = .22$
Anxiety at enrollment—Zung	35.93 (7.28)	36.17 (8.40)	$t(25) = .08$	$p = .94$
MHI global mental health index score at enrollment	155.53 (18.27)	144.67 (32.29)	$t(25) = -1.10$	$p = .28$

Results are presented as mean (SD), unless noted otherwise. No significant differences between treatment group and placebo group were observed

t independent two group Student's *t* test, *CES-D* Center for Epidemiologic Studies–Depression, *MHI* Mental Health Inventory, *SD* standard deviation

[a] One subject was excluded from the analysis

*Fisher exact test

mental well-being during fertility treatments and possibly improve their treatment outcomes.

The design of our study is that of a placebo-controlled trial. Placebo treatment has been shown to have a significant therapeutic effect in depression studies which may partly obliterate the effect of the active drug. Studies show that this effect was pronounced especially for lower baseline depression severity (Khin et al. 2011). Nevertheless, our small sample size did not seem to affect the findings. Despite a low baseline symptom severity in our study, and contrary to the findings mentioned above, our results demonstrated a significant difference between the treatment and placebo groups regarding subjective levels of depression and anxiety and subscales of the MHI questionnaire which emphasizes the strength of our findings.

There are a number of limitations to the current study. The principal limitation is the small sample size recruited. Unfortunately, only one patient in every group had a positive pregnancy test, which eliminated our ability to address the interaction between patients' mental well-being and pregnancy achievement rates. Low pregnancy achievement rates may

Table 3 Comparison of the sample psychological characteristics on the day of embryo transfer ($N = 27$)

	Treatment group ($N = 15$)	Placebo group ($N = 12$)	T value	p
Depression-CES-D	6.40 (6.71)	15.83 (8.69)	3.18	$p = .004$
Anxiety-Zung	27.47 (4.29)	33.17 (6.95)	2.62	$p = .015$
MHI anxiety subscale	15.33 (4.01)	22.58 (7.92)	2.89	$p = .011$
MHI depression subscale	6.53 (1.99)	9.92 (3.20)	3.36	$p = .002$
MHI loss of behavioral/emotional control subscale	12.73 (3.35)	18.58 (6.36)	2.88	$p = .011$
MHI general positive affect subscale	42.4 (8.37)	33.50 (11.69)	−2.30	$p = .030$
MHI emotional ties subscale	9.73 (2.19)	7.33 (3.02)	−2.31	$p = .032$
MHI life satisfaction subscale	4.47 (.64)	3.42 (1.24)	−2.66	$p = 0.17$
MHI psychological distress global scale	38.60 (9.65)	56.75 (17.81)	3.38	$p = .002$
MHI psychological well-being global scale	61.53 (10.72)	47.92 (16.52)	−2.47	$p = 0.24$
MHI a global mental health index score	189.93 (19.56)	158.17 (33.26)	−2.93	$p = .009$

Results are presented as mean (SD), unless noted otherwise. Higher scores in this scale on general positive affect, emotional ties, and life satisfaction MHI subscales indicate positive states of mental health. Higher scores on anxiety, depression, and loss of behavioral/emotional control MHI subscales indicate negative states of mental health. Higher scores on the global MHI score indicate greater psychological well-being

CES-D Center for Epidemiologic Studies–Depression, *MHI* Mental Health Inventory

Table 4 Comparison of the psychological characteristics between treatment and placebo groups at enrollment and embryo transfer time points ($N = 27$)

	Enrollment day (T1)				Embryo transfer (T2)			
	Treatment group ($n = 15$)	Placebo group ($n = 12$)	Statistical test	p	Treatment group ($n = 15$)	Placebo group ($n = 12$)	Statistical test (t)	p
CES-D	19.60 (9.70)	24.33 (9.58)	1.27	NS	6.40 (6.71)	15.83 (8.69)	3.18	$p = .004$
Zung	35.93 (7.28)	36.17 (8.40)	0.08	NS	27.47 (4.29)	33.17 (6.95)	2.62	$p = .015$

Results are presented as mean (SD), unless noted otherwise

t independent two group Student's *t* test, *CES-D* Center for Epidemiologic Studies–Depression, *SD* standard deviation, *NS* nonsignificant

be attributed to the mean high age of the participants in the study; 44.6 years for the treatment group and 41.8 years for the placebo group. According to data from the Israeli ministry of health, the pregnancy achievement success rate for a single IVF cycle at the age of 40 is 17%, while at the age of 44, rates drop to 4%. Nevertheless, even with a small sample size, a significant difference was found regarding the psychometric parameters. Another limitation is that our sample varied broadly in the infertility diagnoses and number of previous treatments prior to joining the current IVF program. This heterogeneity in women's infertility diagnosis and treatment history precludes assessment of mental symptomatology which may differ in specific patient groups. To address this, future investigations should either include samples of large enough size to enable statistical analyses stratified by infertility diagnosis or include only women with one particular diagnosis.

In summary, our findings suggest that a short-term treatment with SSRI may serve as a preventive treatment against depressive and anxiety symptoms in women undergoing IVF treatments. This finding was observed even though most women were only mildly symptomatic. Further studies concerning pharmacological interventions in larger samples are still needed for deeper exploration of the subject. Furthermore, studies addressing the issue of screening for psychological and physiological stress indicators in women undergoing infertility treatments are in order. Routine screening may promote psychological and pharmacological interventions that may prove helpful changing psychological parameters and their physiological parallels that sabotage the final aim at achieving a healthy pregnancy.

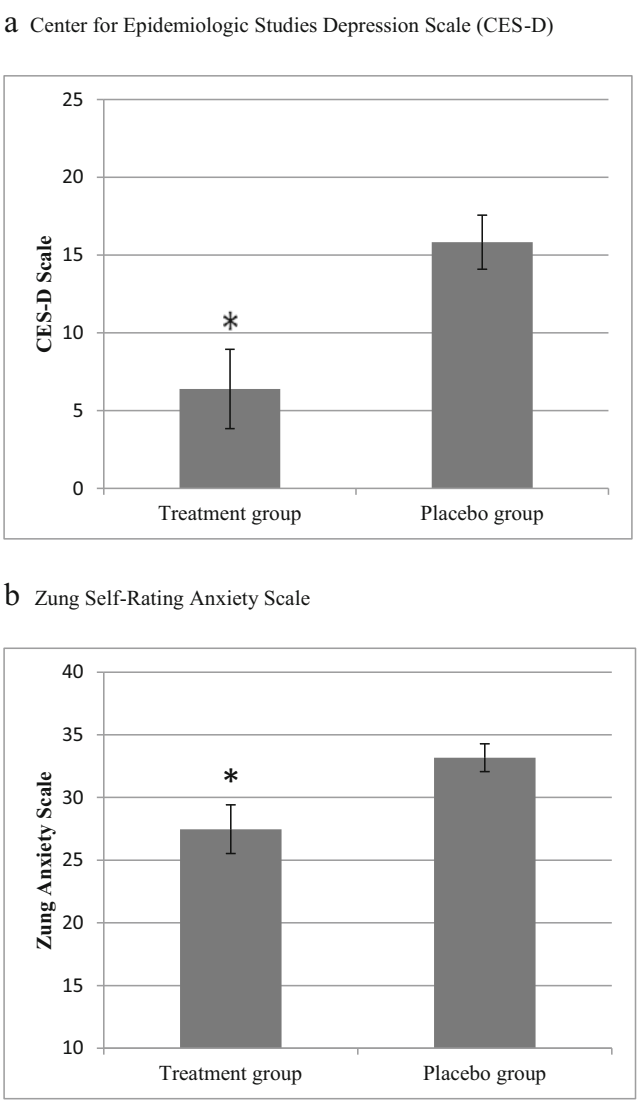

Fig. 2 Mean scores on mood (CES-D) and anxiety (Zung) questionnaires at time of embryo transfer. **A** Center for Epidemiologic Studies Depression Scale (CES-D). **B** Zung Self-Rating Anxiety Scale

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Compliance with ethical standards

All procedures performed in study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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

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