Psychological Response and Cortisol Reactivity to In Vitro Fertilization Treatment in Women With a Lifetime Anxiety or Unipolar Mood Disorder Diagnosis

Inbar Zaig, MA; Foad Azem, MD; Shaul Schreiber, MD; Ami Amit, MD; Yael Gottlieb Litvin, MA; and Miki Bloch, MD

ABSTRACT

Objective: Knowledge regarding the emotional and physiologic response of women with psychiatric disorders undergoing in vitro fertilization (IVF) treatments is rather limited. We evaluated psychological adjustment and cortisol reactivity to IVF treatment in women with a lifetime diagnosis of a unipolar mood or anxiety disorder compared to those without such a diagnosis.

Method: Women undergoing IVF treatments (N = 121) were interviewed from January 2006 to December 2007 to assess for the presence of a history of a lifetime *DSM-IV-TR* unipolar mood or anxiety disorder. They were evaluated prospectively at baseline, at ovulation, and before the pregnancy test. Primary outcome measures included assessments of depressive and anxiety symptoms (Center for Epidemiologic Studies Depression Scale and State-Trait Anxiety Inventory, respectively) and plasma cortisol levels.

Results: Of 108 participants included in the study, 19.4% (n = 21) were determined to have a lifetime Axis I unipolar mood or anxiety diagnosis. Women with lifetime Axis I psychopathology showed significantly greater symptom elevation for depression ($F_{2,194} = 10.97$, $P < .001$) and for anxiety ($F_{2,194} = 3.4813$, $P = .033$) compared to the group without psychopathology. A different physiologic pattern was observed for cortisol response: whereas the group without psychopathology responded physiologically to the stressful treatment with continuously elevated cortisol levels, a blunted cortisol response was observed for the group with lifetime psychopathology ($F_{2,200} = 2.9$, $P = .05$).

Conclusions: Women diagnosed with a lifetime unipolar mood or anxiety disorder developed robust symptom exacerbation during IVF treatment compared to women without an Axis I diagnosis. Conversely, the women with a lifetime diagnosis are characterized by a blunted cortisol response, indicating a pattern of dissociation between the robust increase in anxiety and depression and cortisol response to the acute psychological stress. This study emphasizes the need for a psychiatric screening prior to IVF treatment and for the utilization of preventive psychiatric and psychological interventions.

Trials Registration: ClinicalTrials.gov identifier: NCT01032421

J Clin Psychiatry 2013;74(4):386–392

Submitted: *March 23, 2012; accepted October 15, 2012 (doi:10.4088/JCP.12m07805).*
Corresponding author: *Miki Bloch, MD, Department of Psychiatry, Tel Aviv Sourasky Medical Center, 6 Weizman Str, Tel Aviv, Israel (mikib@tasmc.health.gov.il).*

Infertility is a widespread condition, affecting 3.5%–16.7% of couples in the Western world.[1] This condition has unique and destructive psychological implications[2] and elicits a variety of negative emotions.[3] Although past or current diagnosed psychiatric disorders are common in women of childbearing age, this factor is generally overlooked in infertility evaluation. The overall prevalence of psychiatric disorders among infertile women has been estimated to be about 40%, compared to about 28% in the fertile population,[4] with anxiety (23%) and depression (17%) being the most common disorders prior to initiation of the IVF procedure.[4,5] Having a history of a psychiatric disorder, whether in the present or in the past, may result in substantial psychological, and possibly physiologic, consequences when the disorder interacts with infertility treatments. Furthermore, understanding such interactions is of importance in clarifying the possible role of psychiatric conditions in the complex physiologic processes that are involved in the outcome of infertility treatments.[6]

Assisted reproductive techniques can evoke substantial psychological sequelae, even to a greater extent than the distress caused by the infertility experience itself.[3,7] In particular, in vitro fertilization (IVF) is a stressful procedure that has unpredictable psychological consequences,[2,8] including increased risk of hospitalization due to the development of an adjustment disorder.[9] In fact, 30% of IVF patients drop out of treatments due to the psychological burden.[10]

As a history of mood disorders is an important predictor for the recurrence of depression consequent to a stressful life event,[11] the IVF procedure may expose vulnerable women to potentially overwhelming psychological consequences. Indeed, women with a history of depression are twice as likely to develop a recurrence of depression during certain reproductive events,[12] and they experience more distress during infertility treatments as compared to controls.[7] Moreover, in women with anxiety disorders, symptoms have been found to intensify subsequent to infertility treatment,[13] increasing the likelihood of dropping out of treatment after only 1 cycle.[14] Thus, it is important to thoroughly understand and predict the emotional response of women with psychiatric diagnoses who are undergoing IVF treatments.

Depressed patients tend to demonstrate abnormal activity of the hypothalamic-pituitary-adrenal (HPA) axis, manifested by high levels of plasma cortisol, inhibition of the HPA axis negative feedback loop, and increased size and activity of the pituitary and adrenal glands.[15] Furthermore, low frequency of gonadotropin-releasing hormone secretion, which can deteriorate to functional hypothalamic amenorrhea, is also observed.[16] In reaction to stress challenges, depressed patients show abnormal HPA responses such as prolonged recovery time of cortisol levels[17] and a lack of suppression of cortisol on the dexamethasone suppression test.[18] Comorbidity

with anxiety disorders is thought to contribute to the abnormal HPA axis reactivity in response to stress challenges,[19] which may be seen even in remitted depressed women.[20] Hence, women with a psychiatric pathology who are undergoing an IVF procedure may also be prone to exhibit abnormal hormonal stress reactivity in response to emotional stress and possibly to the hormonal manipulations utilized. Indeed, in a previous study,[21] we demonstrated that in women with a history of postpartum depression, more than in controls, induction of supraphysiologic levels of gonadal hormones enhanced secretion of cortisol.

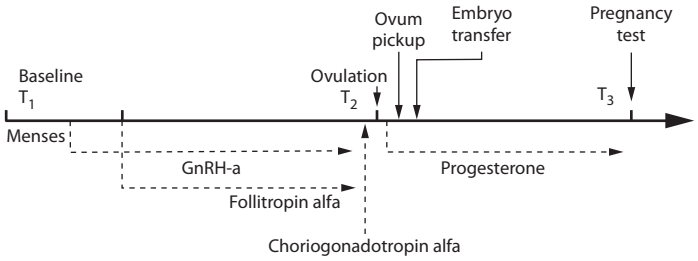
Abnormal HPA axis reactivity among psychologically vulnerable women at such a critical and demanding time in life may result in substantial consequences. It has been theorized that interaction between abnormal HPA axis reactivity and hypothalamic-pituitary-gonadal axis fluctuations is a key factor in the induction of depression in vulnerable women.[22] Moreover, in recent years, some evidence suggests a negative impact of elevated HPA axis products on conception in IVF treatments. For example, Csemiczky et al[23] found that cortisol levels were higher throughout the IVF cycle in women who did not conceive compared to those who did. Therefore, any malfunction of the HPA axis in women with a lifetime Axis I diagnosis may have psychological and physiologic implications in IVF treatments, as well as a possible effect on outcomes.

In the present prospective longitudinal study, we evaluated depressive and anxiety symptom exacerbation and cortisol reactivity during an IVF treatment cycle in women with a lifetime diagnosis of a unipolar mood or anxiety disorder versus women without a psychiatric disorder.

Clinical Points

- Women undergoing in vitro fertilization (IVF) have a high prevalence (about 20%) of lifetime unipolar mood and anxiety psychopathology.
- In contrast to women without lifetime psychopathology, those with a formal diagnosis of unipolar mood or anxiety disorder develop significant symptom exacerbation throughout an IVF treatment cycle.
- It is of significant clinical value to identify women with a history of such psychopathology prior to the fertility treatment so that they can be followed up and possibly treated as needed.

Figure 1. Schematic Timeline for an In Vitro Fertilization Cycle With Study Time Points[a]



[a]Study time points are as follows: T_1 = baseline, before entering treatment; T_2 = end of the 2-week gonadotropin administration period and at ovulation induction; T_3 = 12 days after embryo transfer and just before blood was drawn for β-human chorionic gonadotropin to determine chemical pregnancy.
Abbreviation: GnRH-a = gonadotropin-releasing hormone agonist.

METHOD

The study was approved by the local institutional review board committee at the Tel Aviv Sourasky Medical Center (ID#04–284) and was registered on ClinicalTrials.gov (identifier: NCT01032421). This study utilized an existing cohort that was reported previously[24] and is based on all eligible women admitted to the IVF unit at the Lis Maternity Hospital, Sourasky Medical Center, Tel Aviv, Israel, from January 2006 to December 2007.

The following inclusion criteria were met by 121 women: (1) first or second IVF/embryo transfer cycle (female/male factor or unexplained infertility) and (2) age < 42 years. Exclusion criteria were (1) endometriosis due to the psychological implications of this condition,[25] (2) psychotherapeutic or psychopharmacologic treatment, (3) past or current diagnosis of psychotic disorder, and (4) current diagnosis of anxiety or unipolar mood disorder according to *DSM-IV-TR* criteria. After complete oral description of the study to the subjects, written informed consent was obtained. Participation of 13 women was terminated due to lack of response to the physiologic procedure (ie, no fertilization due to lack of estrogen response, etc [n = 8] or lack of cooperation [n = 5]). Dropouts and participants did not differ significantly on any parameters except the number of years for which the fertility problem had been known: a mean of 4.6 years for dropouts and 2.6 years for the participants ($t_{104} = -2.33$, $P = .02$).

Participants were assigned to a conventional IVF protocol (Figure 1) and were comparable in terms of demographic and clinical parameters. Blood was drawn and participants were asked to complete questionnaires at 3 data collection points: before entering the treatment (T_1), at the end of the 2-week gonadotropin administration period (2–4 weeks after baseline) and at ovulation induction (T_2), and 12 days after embryo transfer just before blood was drawn for β-human chorionic gonadotropin to determine chemical pregnancy, before the outcome of the test was known to the woman (T_3). Research method and subject depiction have been reported in detail in a previous article.[24]

Measures

Hormonal measures. Blood samples were collected between 08:00 h and 10:00 h in tubes containing ethylenediaminetetraacetic acid (EDTA) and immediately centrifuged and stored at −80°C until assayed. Serum measurements of cortisol, estradiol, and progesterone were performed with commercial kits (electrochemiluminescence immunoassay [Elecsys 2010; Roche Diagnostics, Basel, Switzerland]). Within- and between-run precision coefficients of variation were 1.4% and 2.1%, respectively, for estrogen and cortisol and 1.2% and 2.0% for progesterone.

Psychiatric diagnostic measures. Psychiatric diagnoses were established using the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID)[26] according to *DSM-IV-TR* criteria. The SCID is a valid tool for establishing an objective psychiatric classification. The interview was performed at baseline (T_1) by our research assistant, a certified psychiatric social worker, who was trained and supervised in the administration of the SCID by a psychiatrist (M.B.).

To measure coping strategies, we used the COPE Inventory,[27] which assesses coping traits.

State psychological measures. Besides plasma cortisol levels, the other primary outcome measures were 2 state mood measures used to assess for anxiety and depression, respectively: the Hebrew versions of the State-Trait Anxiety Inventory (STAI)[28] and the Center for Epidemiologic Studies Depression Scale (CES-D).[29] The internal-consistency coefficients for the sample in the present study were Cronbach α values of 0.882 and 0.78 for STAI and CES-D, respectively.

To provide an overview of the patients' symptoms, the Hebrew version of the Brief Symptom Inventory (BSI)[30] was issued. It is composed of 9 symptom dimensions and 3 global indexes: the Positive Symptom Total (PST), reflecting the number of reported symptoms; the Positive Symptom Distress Index (PSDI), measuring the intensity of symptoms; and the Global Severity Index (GSI), which combines the number of symptoms and their severity, thus measuring overall psychological distress. The internal-consistency coefficients for the sample in the present study were Cronbach α values ranging from 0.57 to 0.77 for the different scales.

Statistical Analysis

Data analysis was performed using the STATISTICA program (version 8.0; StatSoft, Tulsa, Oklahoma). Means and standard deviations were used as descriptive statistics. Comparisons between the 2 study groups were made using χ^2 test for nominally scaled variables, Kruskal-Wallis test for ordinal variables, and 2-tailed *t* test for continuous variables. Pearson correlation coefficients were calculated for continuous variables. A 2 × 3 repeated-measures analysis of variance (ANOVA) was used (group × time) to investigate both main effects of group affiliation and interaction effects for changes in the 2 groups over the treatment time. Post hoc analysis was conducted using the Tukey range test. All significance tests were 2-sided and performed at a required significance level of .05.

RESULTS

Of the 108 participants included in the study, a total of 21 women (almost 20%) were diagnosed as suffering from a lifetime Axis I unipolar mood or anxiety disorder: 10 women were diagnosed with a mood disorder (9 major depressive disorder and 1 with dysthymia), 10 were diagnosed with an anxiety disorder (4 with panic disorder, 3 with generalized anxiety disorder, 2 with simple phobia, 1 with obsessive-compulsive disorder), and 1 was diagnosed with both major depressive disorder and generalized anxiety disorder.

In light of the small subgroups, we aggregated all 21 women who experienced mental illness into 1 "psychopathology" (PP) group. The PP group did not differ from the "no psychopathology" (no-PP) group in any of the sociodemographic characteristics (eg, age, education, marital and familial status, employment status), past psychological treatments, or infertility history measures (eg, duration of known infertility, number of previous IVF cycles) except for 2 variables: women with PP were slightly less educated than the no-PP group (Kruskal-Wallis test: $P = .036$) and reported lower income (Kruskal-Wallis test: $P = .01$).

Stress Reactivity—Psychological

The full group of women showed a significant increase in depressive (CES-D) and anxiety (STAI) symptoms over the treatment cycle (time effect for depression: $F_{2,194} = 21.99$, $P < .001$; anxiety: $F_{2,194} = 19.64$, $P < .001$). Women with psychopathology (PP group) showed a significantly greater elevation in both depression (interaction effect for group × time: $F_{2,194} = 10.97$, $P < .001$) and anxiety ($F_{2,194} = 3.4813$, $P = .033$) compared to the no-PP group (Table 1). Post hoc analysis revealed that both groups showed considerable, yet similar, distress at the beginning of the treatment, with no between-group differences at T_1 for depression ($P = .9$) or anxiety ($P = .5$). When the medical treatment progressed, the PP group reacted with a significant increase in distress, whereas no-PP women maintained a relatively steady mental state (between-group differences at T_2: depression, $P < .01$; anxiety, $P < .01$; at T_3: depression, $P < .01$; anxiety, $P < .01$) (Figure 2).

When the PP group was analyzed separately, a significant correlation between baseline depression scores and T_3 depression scores was found ($r = 0.66$, $P = .002$). However, no correlation was found between baseline levels of depression or anxiety and the extent of increase (Δ) in distress from baseline to the T_3 time point (depression, $r = -0.18$, $P = .45$; anxiety, $r = 0.37$, $P = .11$). Hence, in the PP group, women with extensive levels of anxiety and depression at baseline showed a similar extent of worsening of symptoms as women who started the treatment with low levels of depression and anxiety.

While we could not assess *DSM*-defined relapse, to assess how many of the women had a clinically significant worsening of symptoms during treatment, we defined a cutoff for significant symptoms as a CES-D score > 21 and STAI score > 40 at the end of treatment (T_3). We found that in the PP group, 5/21 women (24%) had above-cutoff levels of depression at baseline, and 10/21 (48%) had above-cutoff levels of depression at T_3, while in the no-PP group, 13/87 (15%) had above-cutoff levels of depression at baseline, and 12/87 (14%) had above-cutoff levels of depression at T_3. Statistically, for the PP group, this change represents a trend toward significance ($\chi^2 = 2.59$, $P = .1$), and for the no-PP group, no significant difference was observed ($\chi^2 = 0.05$, $P = .8$).

Other Psychiatric Symptoms

Repeated-measures ANOVA (group × time) revealed significant main effects for group for every BSI scale, with

Table 1. Psychological Variables Across Time Points for the Psychopathology (PP, n = 21) and No Psychopathology (no-PP, n = 87) Groups

	Before Entering Treatment (T_1)		At Ovulation Induction (T_2)		Before Pregnancy Test (T_3)			
Measure	Mean	SD	Mean	SD	Mean	SD	$F_{2,198}$	P[a]
Depression—CES-D								
PP	12.95	9.46	22.68	11.10	24.00	11.90	10.97	<.001
No-PP	10.71	7.73	12.26	8.00	12.70	9.62		
Anxiety—STAI								
PP	42.89	9.05	50.84	11.20	52.63	11.80	3.48	<.05
No-PP	38.20	9.26	41.09	11.00	42.37	11.30		
BSI								
Somatization								
PP	0.55	0.54	0.97	0.81	1.13	0.80	1.47	NS
No-PP	0.37	0.50	0.57	0.64	0.68	0.73		
Obsessive-compulsive								
PP	0.72	0.74	1.36	0.98	1.31	1.06	9.86	<.001
No-PP	0.51	0.56	0.62	0.66	0.53	0.65		
Interpersonal sensitivity								
PP	0.33	0.51	0.70	0.78	0.73	0.77	9.89	<.001
No-PP	0.24	0.41	0.16	0.42	0.21	0.40		
Depression								
PP	0.81	0.71	1.11	0.79	0.99	0.75	1.46	NS
No-PP	0.37	0.41	0.44	0.51	0.47	0.56		
Anxiety								
PP	0.93	0.84	1.30	0.75	1.35	0.90	2.86	.06
No-PP	0.59	0.48	0.66	0.61	0.70	0.67		
Hostility								
PP	0.84	0.76	1.19	0.73	0.95	0.69	4.18	<.05
No-PP	0.56	0.54	0.54	0.53	0.49	0.58		
Phobic anxiety								
PP	0.57	0.54	0.92	0.72	0.88	0.69	2.94	.06
No-PP	0.31	0.39	0.39	0.53	0.39	0.54		
Paranoid ideation								
PP	0.69	0.81	0.88	0.82	0.77	0.83	2.35	NS
No-PP	0.37	0.44	0.32	0.48	0.26	0.44		
Psychoticism								
PP	0.59	0.86	0.93	0.83	0.98	0.86	4.62	<.05
No-PP	0.32	0.40	0.39	0.46	0.36	0.44		
Global Severity Index								
PP	0.09	0.59	0.11	0.69	0.12	0.69	5.81	<.05
No-PP	0.05	0.35	0.05	0.43	0.06	0.48		
Positive Symptom Total								
PP	19.29	12.30	26.43	14.80	26.57	15.00	3.2	<.05
No-PP	14.03	9.96	15.93	11.30	15.45	12.90		
Positive Symptom Distress Index								
PP	1.61	0.65	1.78	0.58	1.75	0.64	0.69	NS
No-PP	1.45	0.39	1.49	0.50	1.46	0.46		

[a]Repeated-measures analysis of variance (group × time).
Abbreviations: BSI = Brief Symptom Inventory, CES-D = Center for Epidemiologic Studies Depression Scale, STAI = State-Trait Anxiety Inventory.

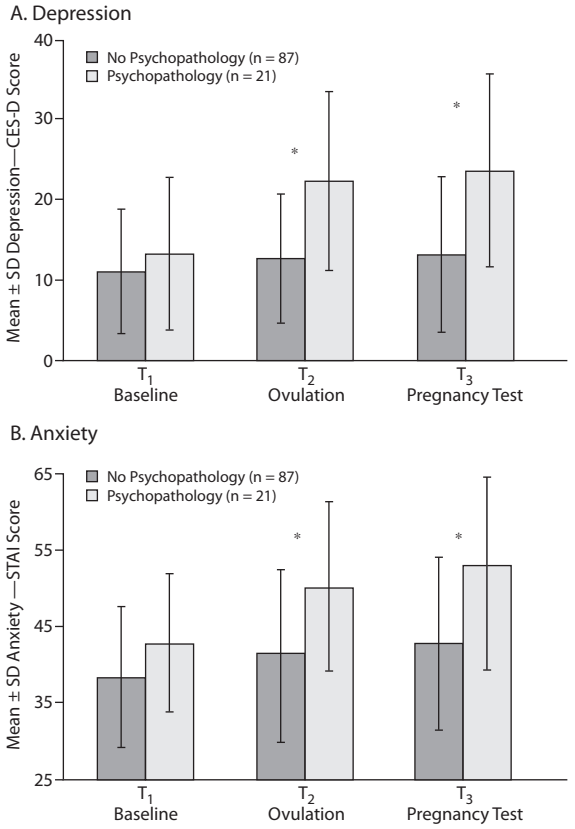
the PP group consistently showing higher psychiatric symptom scores than the no-PP group for somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism, PST, PSDI, and GSI. Significant interaction effects (group × time) are presented in Table 1 and indicate a greater increase in some of the symptoms from baseline to T_2 for the PP group.

We did not find a significant effect of marital status on worsening of depressive or anxiety symptoms during treatment. Furthermore, no correlation was observed on the COPE Inventory between the tendency to receive emotional social support and an increase in anxiety ($r = -0.15$) or depressive symptoms ($r = -0.04$) during the treatment. The same was true when the correlation was tested between the tendency to receive instrumental social support and the worsening of symptoms (anxiety: $r = -0.05$, depression: $r = -0.03$).

Gonadal Hormone Reactivity

Both groups responded adequately to the hormonal manipulation induced by the IVF procedure and did not differ in gonadal hormone responses. As expected, a significant increase in estrogen was observed during gonadotropin stimulation (T_2), and a significant increase in progesterone level was observed at T_3 in all women due to treatment with micronized progesterone and specifically secondary to pregnancy (achieved in 39 of the 108 participants). The PP and no-PP groups did not differ in their hormonal reactivity to the IVF manipulation (for estrogen: $F_{2,194} = 0.4$, P = NS; for progesterone: $F_{2,190} = 2.28$, P = NS).

Figure 2. Depression and Anxiety Symptom Severity in Patients With or Without Psychopathology During 1 In Vitro Fertilization Treatment Cycle[a]



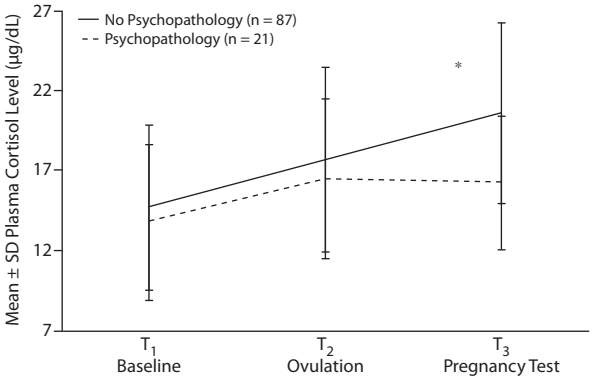
[a]Repeated-measures analysis of variance (group × time) was significant for depression ($F_{2,194} = 10.975$, $P < .0001$) and anxiety ($F_{2,194} = 3.4813$, $P = .033$).
*$P < .01$.
Abbreviations: CES-D = Center for Epidemiologic Studies Depression Scale, STAI = State-Trait Anxiety Inventory.

We previously reported some significant correlations between gonadal steroids and psychological symptoms for the entire sample.[21] When correlations were evaluated specifically for the PP group, we found no significant correlations between progesterone or estrogen levels and any of the psychological symptoms at each of the study's evaluation points.

Stress Reactivity—Cortisol

The entire sample showed progressive elevation of cortisol levels from T_1 to T_2, reaching a peak at T_3. A significant main effect was found for cortisol, indicating that across all points, the PP group had a significantly lower mean cortisol level than the no-PP group (main effect for cortisol: $F_{1,100} = 5.13$, $P = .026$). Further analysis revealed an interaction effect (time × group for cortisol: $F_{2,200} = 2.9$, $P = .05$), indicating a different physiologic response pattern. Post hoc analysis showed similar levels of cortisol for both the PP and no-PP groups at T_1 (mean PP cortisol = 13.74 ± 5.90 μg/dL, no-PP cortisol = 14.64 ± 5.18 μg/dL; $P = .98$) and at T_2 (mean PP cortisol = 16.48 ± 7.90 μg/dL, no-PP cortisol = 17.71 ± 8.30 μg/dL; $P = .88$). However, a significant between-group difference was observed at T_3. Whereas the no-PP group responded physiologically to the stressful treatment with continuously elevated cortisol levels, the PP group showed a blunted response (mean PP cortisol = 16.24 ± 8.43 μg/dL, no-PP cortisol = 20.58 ± 9.22 μg/dL; $P = .01$) (Figure 3).

Figure 3. Plasma Cortisol Levels in Patients With or Without Psychopathology During 1 In Vitro Fertilization Cycle[a]



[a]Repeated-measures analysis of variance (group × time) was significant: $F_{2,200} = 2.8$, $P = .05$.
*$P = .01$, psychopathology vs no psychopathology.

DISCUSSION

The present study is, to our knowledge, the first to show that women diagnosed with a lifetime unipolar mood or anxiety disorder develop robust symptom exacerbation while undergoing an IVF treatment cycle compared to women without an Axis I diagnosis. The increase in depressive and anxiety symptoms and overall global distress indexes was observed in the PP group at 2 points in the IVF cycle, prior to ovulation and embryo pickup (T_2) and to a greater extent before the pregnancy test (T_3) (see Table 1). As opposed to this pattern, women without such a diagnosis showed no detrimental psychological effect of the treatment despite having similar baseline distress levels. Furthermore, while women did not differ in depression or anxiety levels at baseline, women in the PP group showed a clear trend for becoming clinically depressed at the end of the treatment cycle, while women in the no-PP group did not. Our data suggest that the lack of significant change in the PP group is probably due to the small sample size, whereas a larger sample size may very well have resulted in clearly significant results.

The observed deterioration in mental condition in women with a lifetime diagnosis of mood and anxiety disorders can be hypothesized to reflect 2 distinct etiologic factors: (1) an excessive affective response to the hormonal burden inherent to the IVF procedure, and (2) an excessive psychological stress reaction to the infertility period and specifically to the stress of the treatment cycle.

Whereas the first hypothesis has some support in the literature regarding increased prevalence of hormone-related mood disorders in women with a past history of depression or anxiety[31] and IVF-related affective symptoms,[32] our findings do not support this, as we saw no correlations between the changes in plasma gonadal steroid levels and elevation

in mood or anxiety symptoms in our study group. However, as our index group was quite small, we cannot definitely rule out this possibility, which warrants further study.

According to Post's[33] kindling/sensitization model, an affective episode can sensitize the brain and amplify vulnerability to further occurrences of pathologic affective reactivity. Studies with remitted depressed patients confirm that dysfunctional patterns of emotional reactivity are stable and persist after remission. In response to stress manipulation, remitted patients demonstrate heightened[20] and persistent[34] negative affect levels, indicating an inherent difficulty in affect regulation. Moreover, as remitted patients remain sensitized to stress, stressful events of a smaller magnitude can trigger a recurrence of depression.[35] Thus, as IVF treatments are known to be powerful stressogenic events, we can speculate that women with a lifetime diagnosis of depression or anxiety may display their increased vulnerability to stress as anxiety and depressive symptoms during treatment.

This finding has far-reaching implications on the management of women undergoing IVF treatments, as many of them are at increased risk for serious emotional deterioration during, and possibly subsequent to, the treatment cycle. Whereas the emotional distress involved in IVF treatments has been well documented, the majority of women do not receive proper treatment,[36] despite review articles showing promising results with regard to successful psychological interventions.[37,38] Our study highlights the necessity of identifying women with vulnerability for depression or anxiety deterioration during IVF treatments and of providing accessible psychological and psychiatric support in fertility clinics for this subgroup of women.

Our incidental finding that a longer duration of infertility was more likely to be associated with dropping out of the study is also noteworthy. This probably reflects the observation that length of infertility diagnosis is routinely associated with increased depressive symptoms, and thus the duration of infertility should also be further studied in the context of symptom exacerbation in women with a prior psychiatric diagnosis.

The second major finding of this study is the different pattern of cortisol secretion in response to treatment that was observed in the 2 study groups. While the no-PP group did not report an elevation in their subjective feelings of anxiety or depression during treatment, a robust physiologic stress response as indicated by elevated cortisol was observed, whereas the PP group demonstrated a robust increase in anxiety and depression during the treatment cycle concurrent with a blunted cortisol response to the acute psychological stress. This pattern is contradictory to previous studies[39] that looked at women undergoing IVF treatment irrespective of psychopathology. In these studies, cortisol levels showed a progressive increase as the treatment advanced, while psychological distress progressively increased in parallel. As in the present sample, no relation was observed with gonadal hormone fluctuations in these studies.

Although anxiety and mood disorders are often associated with heightened HPA reactivity after exposure to acute stress, findings are inconclusive.[40] For example, studies reveal lower cortisol levels both in the morning and in response to a stress test in women remitted from depression compared to never-depressed women.[41] Patients with panic disorder showed a nonresponse pattern of cortisol secretion under massive psychological stress as opposed to healthy controls.[42] According to recent developmental models,[43] such patterns may reflect inherent habituation of HPA axis functioning in chronically stressed patients. Prolonged exposure to stress can cause hyperactive stress system functioning, ie, enduring increased levels of glucocorticoids, bringing into play adjustment mechanisms such as increased negative feedback sensitivity at the pituitary and hypothalamus levels, resulting in hypoactive HPA axis reactivity.[40,43] Thus, differences between patients and healthy controls may not be noticed under normal conditions, but, rather, only under stressed conditions.[40] Indeed, in the present study, both the PP and no-PP groups showed similar levels of plasma cortisol at baseline (T_1), and a differential response of the HPA axis was observed only when an acute psychological stressor was introduced and the system was challenged. We found no correlation between plasma cortisol levels and either anxiety or depressive symptoms in both groups, and thus a direct cause-effect association between the physiologic and psychological response could not be determined.

Despite the robust differences observed between the 2 groups for both psychological and physiologic responses, the small sample size of women with a psychiatric diagnosis is a definite limitation of the study. This limitation prevented us from looking separately at women who have a lifetime mood disorder versus those with an anxiety disorder, 2 disorder clusters that can perhaps evoke a different response. However, in our opinion, grouping the mood and anxiety disorders together is reasonable, as in both cases the chronic course is characterized by residual symptoms.[44,45] Another limitation of this study is related to the fact that cortisol was collected under naturalistic and nonideal conditions, within a wide 2-hour time window and with no control over time since awakening or food intake. Thus, these data should be viewed with caution, and further investigations using a more stringent design are warranted.

In conclusion, we demonstrated that women undergoing IVF treatments who are diagnosed with a lifetime unipolar mood or anxiety disorder exhibit high levels of distress and a variety of psychiatric symptoms that dramatically increase throughout the treatment cycle. Moreover, they experience a singular pattern of blunted physiologic stress reaction in response to the emotional distress, which is in dissociation with the psychiatric stress response. The findings of this study emphasize the need for a thorough psychiatric screening prior to IVF treatment and possibly for the utilization of preventive psychiatric and psychological interventions. Furthermore, the psychological and physiologic consequences of IVF treatment in women with psychiatric diagnoses should be studied with regard to their possible effects on infertility treatment outcomes. Future investigations should continue to thoroughly assess the psychological, hormonal, and

physiologic outcomes (such as number of retrieved and fertilized oocytes, chemical pregnancy, and a take-home baby) of the psychiatric population attending fertility treatments.

Author affiliations: Department of Psychiatry (Ms Zaig; Drs Azem, Schreiber, and Bloch; and Mr Litvin) and IVF Unit, Lis Women's Hospital (Drs Azem and Amit), Tel Aviv Souraski Medical Center; and Sackler Faculty of Medicine, Tel Aviv University (Drs Azem, Schreiber, Amit, and Bloch and Mr Litvin), Tel Aviv, Israel.
Potential conflicts of interest: None reported.
Funding/support: This study was funded by grant 205-05-06 from the National Institute for Psychobiology in Israel.
Previous presentation: The study was presented in part at the Israel Society for Biological Psychiatry Annual Meeting; March 29–31, 2011; Hagoshrim, Israel.
Acknowledgments: The authors acknowledge the assistance of Irit Bluvstein, PhD, and Hadas Meiboom, MA, from the Department of Psychiatry, Tel Aviv Souraski Medical Center, in coordinating the study, and Igal Ayal, DBA, head of the marketing section in the School of Management and Economics at Tel Aviv-Yaffo Academic College, for helpful comments on the manuscript. None of these individuals report any potential conflicts of interest.

REFERENCES

1. Boivin J, Bunting L, Collins JA, et al. International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. *Hum Reprod*. 2007;22(6):1506–1512.
2. Jurado RA, Moreno-Rosset C, Rio CJ, et al. Principal psychological disorders associated with infertility. *Papeles del Psicólogo*. 2008;29(2):167–175.
3. Cousineau TM, Domar AD. Psychological impact of infertility. *Best Pract Res Clin Obstet Gynaecol*. 2007;21(2):293–308.
4. Chen TH, Chang SP, Tsai CF, et al. Prevalence of depressive and anxiety disorders in an assisted reproductive technique clinic. *Hum Reprod*. 2004;19(10):2313–2318.
5. Williams KE, Marsh WK, Rasgon NL. Mood disorders and fertility in women: a critical review of the literature and implications for future research. *Hum Reprod Update*. 2007;13(6):607–616.
6. Boivin J, Griffiths E, Venetis CA. Emotional distress in infertile women and failure of assisted reproductive technologies: meta-analysis of prospective psychosocial studies. *BMJ*. 2011;342:d223.
7. Burns LH. Psychiatric aspects of infertility and infertility treatments. *Psychiatr Clin North Am*. 2007;30(4):689–716.
8. Verhaak CM, Smeenk JMJ, Evers AWM, et al. Women's emotional adjustment to IVF: a systematic review of 25 years of research. *Hum Reprod Update*. 2007; 13(1):27–36.
9. Yli-Kuha AN, Gissler M, Klemetti R, et al. Psychiatric disorders leading to hospitalization before and after infertility treatments. *Hum Reprod*. 2010; 25(8):2018–2023.
10. Olivius C, Friden B, Borg G, et al. Why do couples discontinue in vitro fertilization treatment? a cohort study. *Fertil Steril*. 2004;81(2):258–261.
11. Rudolph KD, Flynn M, Abaied J, et al. Why is past depression the best predictor of future depression? stress generation as a mechanism of depression continuity in girls. *J Clin Child Adolesc Psychol*.2009; 38(4):473–485.
12. Soares CN, Zitek B. Reproductive hormone sensitivity and risk for depression across the female life cycle: a continuum of vulnerability? *J Psychiatry Neurosci*. 2008;33(4):331–343.
13. Williams KE, Zappert LN. Psychopathology and psychopharmacology in the infertile patient. In: Covington SN, Burns LH, eds. *Infertility Counseling: A Comprehensive Handbook for Clinicians*. 2nd ed. New York, NY: Cambridge University Press; 2006:97–116.
14. Domar AD. Impact of psychological factors on dropout rates in insured infertility patients. *Fertil Steril*. 2004;81(2):271–273.
15. Nemeroff CB, Vale WW. The neurobiology of depression: inroads to treatment and new drug discovery. *J Clin Psychiatry*. 2005;66(suppl 7):5–13.
16. Marcus MD, Loucks TL, Berga SL. Psychological correlates of functional hypothalamic amenorrhea. *Fertil Steril*. 2001;76(2):310–316.
17. Burke HM, Davis MC, Otte C, et al. Depression and cortisol responses to psychological stress: a meta-analysis. *Psychoneuroendocrinology*. 2005;30(9): 846–856.
18. Lopez-Duran NL, Kovacs M, George CJ. Hypothalamic-pituitary-adrenal axis dysregulation in depressed children and adolescents: a meta-analysis. *Psychoneuroendocrinology*. 2009;34(9):1272–1283.
19. Young EA, Abelson JL, Cameron OG. Effect of comorbid anxiety disorders on the hypothalamic-pituitary-adrenal axis response to a social stressor in major depression. *Biol Psychiatry*. 2004;56(2):113–120.
20. Bagley SL, Weaver TL, Buchanan TW. Sex differences in physiological and affective responses to stress in remitted depression. *Physiol Behav*. 2011; 104(2):180–186.
21. Bloch M, Rubinow DR, Schmidt PJ, et al. Cortisol response to ovine corticotropin-releasing hormone in a model of pregnancy and parturition in euthymic women with and without a history of postpartum depression. *J Clin Endocrinol Metab*. 2005;90(2):695–699.
22. Brummelte S, Galea LAM. Depression during pregnancy and postpartum: contribution of stress and ovarian hormones. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010;34(5):766–776.
23. Csemiczky G, Landgren BM, Collins A. The influence of stress and state anxiety on the outcome of IVF-treatment: psychological and endocrinological assessment of Swedish women entering IVF-treatment. *Acta Obstet Gynecol Scand*. 2000;79(2):113–118.
24. Bloch M, Aharonov I, Ben Avi I, et al. Gonadal steroids and affective symptoms during in vitro fertilization: implication for reproductive mood disorders. *Psychoneuroendocrinology*. 2011;36(6):790–796.
25. Gao X, Yeh YC, Outley J, et al. Health-related quality of life burden of women with endometriosis: a literature review. *Curr Med Res Opin*. 2006;22(9):1787–1797.
26. First MB, Spitzer RL, Gibbon M, et al. *User's Guide for the Structured Clinical Interview for DSM-IV Axis I Disorders*. Washington, DC: American Psychiatric Press, Inc; 1997.
27. Carver CS, Scheier MF, Weintraub JK. Assessing coping strategies: a theoretically based approach. *J Pers Soc Psychol*. 1989;56(2):267–283.
28. Spielberger CD, Gorsuch RL, Lushene RE. *Test Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press; 1970.
29. Radloff LS. The CES-D scale: a self report depression scale for research in the general population. *Appl Psychol Meas*. 1977;1(3):385–401.
30. Derogatis LR, Melisaratos N. The Brief Symptom Inventory: an introductory report. *Psychol Med*. 1983;13(3):595–605.
31. Freeman EW. Associations of depression with the transition to menopause. *Menopause*. 2010;17(4):823–827.
32. Warnock JK, Bundren JC, Morris DW. Depressive mood symptoms associated with ovarian suppression. *Fertil Steril*. 2000;74(5):984–986.
33. Post RM. Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. *Am J Psychiatry*. 1992;149(8):999–1010.
34. Gilboa E, Gotlib IH. Cognitive biases and affect persistence in previously dysphoric and never-dysphoric individuals. *Cogn Emotion*. 1997;11(5–6): 517–538.
35. Stroud CB, Davila J, Hammen C, et al. Severe and nonsevere events in first onsets versus recurrences of depression: evidence for stress sensitization. *J Abnorm Psychol*. 2011;120(1):142–154.
36. Volgsten H, Skoog Svanberg A, Ekselius L, et al. Prevalence of psychiatric disorders in infertile women and men undergoing in vitro fertilization treatment. *Hum Reprod*. 2008;23(9):2056–2063.
37. de Liz TM, Strauss B. Differential efficacy of group and individual/couple psychotherapy with infertile patients. *Hum Reprod*. 2005;20(5):1324–1332.
38. Hämmerli K, Znoj H, Barth J. The efficacy of psychological interventions for infertile patients: a meta-analysis examining mental health and pregnancy rate. *Hum Reprod Update*. 2009;15(3):279–295.
39. Tica VI, Mares P, Gouzes C, et al. The variation of serum cortisol during ovarian stimulation for in vitro fertilization. *Gynecol Endocrinol*. 2008;24(1): 12–17.
40. Kudielka BM, Wüst S. Human models in acute and chronic stress: assessing determinants of individual hypothalamus-pituitary-adrenal axis activity and reactivity. *Stress*. 2010;13(1):1–14.
41. Ahrens T, Deuschle M, Krumm B, et al. Pituitary-adrenal and sympathetic nervous system responses to stress in women remitted from recurrent major depression. *Psychosom Med*. 2008;70(4):461–467.
42. Petrowski K, Herold U, Joraschky P, et al. A striking pattern of cortisol non-responsiveness to psychosocial stress in patients with panic disorder with concurrent normal cortisol awakening responses. *Psychoneuroendocrinology*. 2010;35(3):414–421.
43. Fries E, Hesse J, Hellhammer J, et al. A new view on hypocortisolism. *Psychoneuroendocrinology*. 2005;30(10):1010–1016.
44. Bystritsky A. Treatment-resistant anxiety disorders. *Mol Psychiatry*. 2006;11(9):805–814.
45. Nierenberg AA, Husain MM, Trivedi MH, et al. Residual symptoms after remission of major depressive disorder with citalopram and risk of relapse: a STAR*D report. *Psychol Med*. 2010;40(1):41–50.

Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Women's Mental Health section. Please contact Marlene P. Freeman, MD, at mfreeman@psychiatrist.com.