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Psychological distress and in vitro fertilization outcome

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Abstract

Objective—To examine whether psychological distress predicts IVF treatment outcome as well as whether IVF treatment outcome predicts subsequent psychological distress.

Design—Prospective cohort study over an 18-month period.

Setting—Five community and academic fertility practices.

Patients—Two hundred and two women who initiated their first IVF cycle.

Interventions—Women completed interviews and questionnaires at baseline and at 4, 10, and 18 months follow-up.

Main Outcome Measures—IVF cycle outcome and psychological distress.

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Results—Using a binary logistic model including covariates (woman's age, ethnicity, income, education, parity, duration of infertility, and time interval), pre-treatment depression and anxiety were not significant predictors of the outcome of the first IVF cycle. Using linear regression models including covariates (woman's age, income, education, parity, duration of infertility, assessment point, time since last treatment cycle, and pre-IVF depression or anxiety), experiencing failed IVF was associated with higher post-IVF depression and anxiety.

Conclusions—IVF failure predicts subsequent psychological distress, but pre-IVF psychological distress does not predict IVF failure. Instead of focusing efforts on psychological interventions specifically aimed at improving the chance of pregnancy, these findings suggest that attention be paid to helping patients prepare for and cope with treatment and treatment failure.

Keywords

In vitro fertilization; psychological distress

INTRODUCTION

The influence of psychological distress on IVF outcome has continued to be the subject of concern, as it has been hypothesized that depression and anxiety may negatively affect hormonal, neuroendocrine, or immunological functioning leading to poor IVF outcomes. However, specific pathways or mechanisms have not been conclusively identified and much of the research has been limited by a variety of methodological problems. These include nonstandardized measures, small sample sizes, cross-sectional designs, examining positive pregnancy test as the only outcome, failure to distinguish first-time IVF patients from those who had already experienced failure, and lack of control for other predictors of IVF outcomes including age, duration of infertility, and parity (1). Recently, two meta-analyses have addressed this topic. Boivin, Griffiths, and Venetis (2) analyzed 14 prospective longitudinal studies examining pre-IVF psychological distress and IVF outcomes and concluded that there was no evidence of an association between psychological stress and IVF outcome. Matthiessen, Frederiksen, Ingerslev and Zachariae (3) reviewed 31 prospective longitudinal studies that included more variability in the quality of study design, outcomes studied, and the definition of psychological distress (e.g., life events). They concluded that there is limited influence of psychological stress and distress on IVF pregnancy rates but noted the paucity of quality studies and small effect sizes.

Compared to research on the influence of psychological distress on IVF outcome, relatively few studies have examined the influence of IVF outcome on subsequent psychological distress. This literature still consists largely of cross-sectional studies (4). The few longitudinal studies that have examined psychological distress pre and post IVF suggest that depression and anxiety increase after IVF failure, with about 10–25% of women at risk for clinically relevant distress after unsuccessful treatment (5–7). Only one study of psychological distress following IVF included a sizable sample of pregnant and non-pregnant women followed longitudinally, to allow comparison of the responses of women who did and did not become pregnant (8). In a Dutch study, Verhaak et al. reported that women whose IVF treatment was unsuccessful experienced an increase in depression and anxiety relative to their pre-IVF psychological status that persisted over the subsequent 6

months since their last attempt. Furthermore, 20% of the patients experienced anxiety and depression in the clinically relevant range. In contrast, women who became pregnant following IVF experienced a decrease in depression and anxiety over the same time period. Anxiety and depression reverted to pre-IVF levels over the subsequent 3–5 years in women who still did not have a baby, whereas women who did have a baby experienced improvements compared to pre-IVF levels (9). No longitudinal studies of IVF failure compared to success have been done on US samples.

The current study addresses whether pre-IVF psychological distress predicts IVF treatment outcome as well as whether IVF treatment outcome predicts subsequent psychological distress in a large cohort of women undergoing IVF in the Western United States. We employed a prospective, longitudinal design in which infertility patients were interviewed before and after their first IVF cycle with repeated standardized assessments of depression and anxiety as well as treatment outcomes. By jointly examining these two questions, we intended to provide a more definitive picture of the relationship between psychological distress and IVF outcomes and thereby identify when psychological support services may be of most value and to help direct our advice to patients as they prepare for treatment.

MATERIALS AND METHODS

Study Population and Protocol

Women were participants in the Fertility Experiences Project, an investigation of the experiences of women and their partners seeking treatment for infertility. Women were recruited from 5 reproductive endocrinology practices over 8 locations in the greater San Francisco Bay Area in 2000–2004. Eligibility criteria included 1) first visit to the fertility clinic, 2) no previous IVF, 3) no hysterectomy or sterilization, 4) no recurrent miscarriage, 5) currently trying to get pregnant with a male partner, and 6) English-speaking. Baseline in-person interviews were scheduled with interested, eligible participants. Baseline interviews were within 3 months of the first clinic visit and before the start of IVF. Participants were sent a questionnaire packet in the mail which was collected at the baseline interview. From a total of 1040 eligible women, baseline interviews were completed with 416 (41.2%), 372 (35.1%) refused, 194 (18.3%) were unable to be contacted, and 58 (5.5%) undertook a fertility treatment procedure before we could conduct their baseline interview. Demographic data recorded at the baseline assessment included the woman’s age, ethnicity, income, educational level, parity, and the number of months the woman had been attempting conception.

Follow-up assessments were conducted at 4, 10, and 18 months following the baseline interview and involved the completion of questionnaires and telephone interviews for each participant. At each follow-up interview, participants were asked 1) whether they had started any IVF cycles or other treatment since the last interview and the start date of that treatment, 2) the current outcome of any IVF cycles or other treatment since the last interview (currently in-cycle, incomplete cycle, negative pregnancy test, positive pregnancy test, miscarriage, termination or delivery) and 3) if they had any non-treatment-related pregnancies since the last interview. At the end of the 18-month study period, medical records were collected for each couple from the physician practice to confirm the presence

of ongoing pregnancies. Participants remained in the study regardless of the treatments they pursued and or where they received their medical care. Retention rates were high, with 96% of the original sample completing the 4-month follow-up, 93% completing the 10-month follow-up and 89% completing the 18-month follow-up.

This report focuses on the 202 study participants who initiated their first IVF cycle at any time during the 18-month study period (donor sperm, donor oocyte, and surrogacy cycles were excluded). The study protocol was approved by our Institutional Review Board and informed, written consent was obtained.

Psychological distress measures

Depression and anxiety were measured at baseline and each assessment point. Depression was measured with the Center for Epidemiologic Study of Depression Scale (CES-D; 10), which measures depressive symptoms and was developed for use in the general population. The CES-D consists of 20 items which are rated using a 4-point ordered response set to indicate how frequently symptoms were experienced during the previous week (0=rarely or none of the time, 3=most or all of the time). Total scores were created for each respondent by summing their item responses, resulting in a measure with a possible range from 0–60 and higher scores indicating more depressive symptoms. Participants with CESD scores >=16 have been considered at risk for clinical depression (11). The test has excellent concurrent validity (levels up to r=.72) and internal consistency (.85 for general population; r=.90 for clinical populations). The current study yielded an internal consistency score of . 90.

Anxiety was measured using the State Anxiety subscale of the State-Trait Anxiety Inventory (STAI; 12). The STAI is a 20-item measure of the intensity of the emotional state characterized by subjective feelings of tension, anxiety, and apprehension during the past week. Responses are made using a 4-point ordered response set ranging from 1 “not at all” to 4 “very much so.” Total scores were created for each respondent by summing their item responses, resulting in a measure with a possible range from 20–80 and higher scores indicating more anxiety symptoms. The test has excellent concurrent validity (levels up to r=.80) and internal consistency (.91 for general populations). A cut-point of 39 is often used as indicative of clinically significant symptoms of state anxiety (13). The current study yielded an internal consistency of .92.

RESULTS

Table 1 summarizes the demographic and reproductive characteristics for the 202 women in the sample who initiated their first IVF cycle during the 18-month study period. The average age was 35, with a range from 24–45. The majority of women were Caucasian, highly educated and had relatively high household incomes. Most had no children and almost half had been attempting conception for more than 2 years. Testing prior to the first IVF cycle found that 28% of women were in the clinical range for depression and 56% were in the clinical range for anxiety. Testing after the first IVF cycle found that 37% of women were in the clinical range for depression and 57% were in the clinical range for anxiety. Across all

women, the overall level of depression increased after IVF, t=2.64, p<.01, whereas the overall level of anxiety remained the same, t=.56, ns.

Did pre-treatment psychological distress predict the outcome of the first IVF cycle?

Pre-treatment depression and anxiety were taken from the assessment point preceding the start of the first IVF cycle. For example, if the IVF cycle was started at month 6, pre-treatment depression and anxiety were taken from the 4-month follow-up. The amount of time between the assessment of psychological distress and the IVF start date was approximately 2 months (mean 68 days, median 60 days, standard deviation 53.94). IVF outcomes were categorized as follows: the "success" group consisted of 57 women (28% overall success rate), including 42 (21%) who had a live delivery as a result of the cycle and 15 (7%) who had an ultrasound-confirmed, ongoing pregnancy as a result of the cycle at the end of the study; the "failure" group consisted of 145 women, including 33 women (16%) who had an incomplete cycle (gonadotropins were started but no oocyte retrieval or no embryo transfer occurred), 84 (42%) who had a negative pregnancy test, and 28 (14%) whose pregnancy ended in miscarriage or termination of a nonviable pregnancy. Table 2 shows the means, standard deviations, and percentages in the clinical range for pre-IVF psychological distress. T-tests revealed that pre-IVF depression was not significantly different in women whose IVF cycles were successful (M=11.29) compared to those whose cycles failed (M=12.39), t=0.71, p=.48. Similarly, t-tests revealed that pre-IVF anxiety was not significantly different in women who IVF cycles were successful (M=39.96) compared to those whose cycles failed (M=41.41), t=0.79, p=.43.

A binary logistic model regressed IVF outcome (failure vs. success) onto pre-treatment depression with covariates including woman's age, ethnicity (white vs. other), income, education, parity, duration of infertility, follow-up assessment point in which IVF cycle was reported (4, 10, or 18 months), time in days between pre-treatment depression assessment and the IVF start date, and the interaction between pre-treatment depression and time in days between pre-treatment depression assessment and the IVF start date. The interaction term was added to examine whether the effect of pre-treatment distress on IVF outcome might depend on how much time had elapsed, such that distress measured closer to the IVF cycle would have a greater impact on outcome than when assessed more distally.

Backward elimination was used to remove all explanatory variables with p-values >.20. Pre-treatment depression was not a significant predictor of IVF outcome, nor was the interaction between pre-treatment depression and the time elapsed between depression assessment and the cycle start date. Woman's age significantly predicted IVF failure, OR=1.09, 95% CI= 1.01–1.17, p < .05. For each additional year, the chance of pregnancy was reduced by 9%. The other covariates (ethnicity, income, education, parity, duration, time elapsed, follow-up assessment) were not significant predictors of IVF outcome.

For pre-treatment anxiety, the model was identical after backward elimination. Pre-treatment anxiety was not a significant predictor of IVF outcome, nor was the interaction between pre-treatment anxiety and the time elapsed between depression assessment and the IVF start date. Woman's age was the only covariate that significantly predicted IVF failure.

Did IVF treatment failure predict subsequent psychological distress?

Examining the same group of 202 women, we used the assessment point in which the first IVF cycle was reported as the index assessment. Treatment outcomes from the period between the previous assessment and the index assessment were used to predict post-treatment psychological distress. Psychological distress measures from the index assessment were the outcome variables. For example, if the first IVF cycle occurred between the 4 month follow-up and the 10 month follow-up, the most recent treatment outcome as of the 10 month follow-up would be the predictor, and 10-month psychological distress would be the outcome. The average time between the most recent treatment cycle and the post-treatment psychological distress assessment was 75 days (standard deviation 48.32, range 0[1]–242 days). Treatment outcomes were summarized in 3 groups: 62 *pregnant*, 103 *treatment failure*, and 37 *currently in-cycle*. The *pregnancy* group consisted of 48 women who were pregnant from their 1st IVF cycle and 14 who had already become pregnant after their first IVF failed (12 from a subsequent IVF cycle, 1 from a subsequent IUI, and 1 non-treatment-related pregnancy). The *treatment failure* group had all failed their first IVF, and 27 had failed more than 1, 12 had failed subsequent IUI or medication-only cycles, and 1 had had a non-treatment-related pregnancy end in miscarriage. The *in-cycle* group consisted of 30 women currently in the midst of their 1st IVF, and 7 currently in the midst of their 2nd IVF cycle. Table 3 shows the means and standard deviations for depression and anxiety for each treatment status group at the index assessment.

We fit linear regression models with backward elimination of all explanatory variables with a *p*-value > .20. Covariates were woman's age, income, education, parity, duration of infertility, follow-up assessment point in which IVF cycle was reported (4, 10, or 18 months), time in days between the most recent treatment cycle and the index assessment, and depression or anxiety at the assessment prior to the index assessment (pre-IVF). Separate models were calculated for depression and anxiety. The reported B values represent the expected change in the outcome for a one-unit increase of the corresponding explanatory variable. For binary explanatory variables (e.g., treatment failure versus currently pregnant), the B values represent the expected outcome difference across the groups defined by the binary predictor. For continuous explanatory variables (pretreatment psychological distress), the B values represent the expected change in the outcome corresponding to a one-unit increase in the explanatory variable.

Pre-IVF depression was associated with higher post-IVF depression (B=0.50, $p < .0001$). Treatment failure was associated with higher post-IVF depression than pregnancy or being currently in cycle, (B=4.48, $p < .001$ and B=7.34, $p<.001$, respectively). The length of time since the most recent treatment cycle was associated with lower post-IVF depression, B= −2.39, $p<.0001$ (for a 30 day increase in time). The other covariates (women's age, income, education, parity, duration, follow-up assessment point) were not significant predictors of post-IVF depression.

[1]0 Days refers to those women who were still in cycle at the post assessment

Pre-IVF anxiety was associated with higher post-IVF anxiety (B=.57, p < .0001). Treatment failure was associated with higher post-IVF anxiety than pregnancy or being currently in cycle (B=5.49, p < .01 and B=8.77, p<.001, respectively). Also, being nulliparous was associated with higher post-IVF anxiety (B=4.89, p < .05). The length of time since the most recent treatment cycle was associated with lower post-IVF anxiety, B=−4.26, p<.0001 (for a 30 day increase in time). The other covariates (women's age, income, education, duration, follow-up assessment point) were not significant predictors of post-IVF depression.

DISCUSSION

This prospective longitudinal study is the first to simultaneously address both the effect of psychological distress on IVF outcome and the effect of IVF outcome on subsequent psychological distress. We present evidence that suggests that IVF failure predicts subsequent psychological distress, but that pre-IVF psychological distress does not predict IVF failure.

With respect to the question of whether pre-IVF psychological distress predicts the outcome of IVF, our finding is consistent with recent studies (14–16) and the two recent meta-analytic reviews (2,3), but contrasts with earlier research showing that psychological distress predicted a higher likelihood of failure (17). The more recent research (including this current study) can be distinguished from most earlier studies by several design improvements including 1) inclusion of only first-time IVF patients, whose emotional experiences were not colored by experience with previous IVF failures, 2) utilization of standardized measures of psychological distress, 3) use of ongoing pregnancy or live birth as outcomes rather than positive pregnancy tests, and 4) inclusion of all patients whose cycles were started, including those that were incomplete. Furthermore, by controlling for known predictors of outcomes including woman's age, duration of infertility, and parity, we have avoided misinterpreting the association between pre-IVF distress and outcome if the predictor was correlated with distress (e.g., if older women, who believed their chances of success were lower, were more anxious, the association between pre-IVF anxiety and later outcome could be falsely inflated).

With regard to the effect of an unsuccessful IVF outcome on psychological distress, we found that, independent of pre-IVF depression and anxiety, women whose cycles failed scored approximately 4 points higher in depression and 5 points higher in anxiety compared to women whose cycles were successful. To our knowledge, this is only the second sizable study to follow IVF patients prospectively from pre-IVF through post-IVF regardless of their treatment outcomes and the first in the United States.

Rates of pre-treatment depression and anxiety were quite high, with over one quarter of women clinically at risk for depression and over half clinically at risk for anxiety before the start of IVF. After failure, the rates for depression increased to almost half and to almost two-thirds for anxiety. While women who became pregnant scored lower in distress than those who failed, 30% remained at risk for depression and 50% remained at risk for anxiety during pregnancy. Even though these self-report measures likely overestimate the number of actual clinical cases of depression and anxiety (18), these findings suggest that

psychological distress before and after IVF is a significant issue. While there is limited comparative data in the existing literature, these rates appear higher than those reported previously, both pre-IVF and post-IVF (6–8, 19,20). In fact, depression scores on the CESD after failure were even higher than those reported for cancer patients during treatment (21) and similar to those reported for parents experiencing death of a child (22). The high rates of psychological distress could have resulted from having conducted this study separately from the medical practices from which participants were recruited, as participants may have felt more comfortable revealing psychological distress, having been assured that their answers would not be seen by their doctors or used to judge their suitability for treatment. The notably high rates could also reflect characteristics of this US sample compared to most previous research conducted in Europe and other countries, perhaps related to the relatively high costs of IVF in the US (23), or to different practice patterns. However, without direct comparison data with other countries, we are unable to propose any definitive explanations.

Despite relatively high levels soon after treatment failure, depression and anxiety appear to decrease over time subsequent to treatment. For depression, a 2-point decline in the CESD was observed per post-treatment month and for anxiety, a 4-point decline in the STAI was observed each month after treatment. This is consistent with studies that showed gradual decreases in depression over longer periods of time (8,9).

Pre-IVF psychological distress was a strong predictor of post-IVF distress. Women who are distressed before IVF are at risk for increases in anxiety and depression after treatment. This finding is consistent with Verhaak (8) who reported that pre-IVF depression was a strong risk factor for continued depression.

Despite the advantages of our prospective, longitudinal design using multiple assessments conducted separately from the medical practices from which participants were recruited, we acknowledge certain limitations. This study is not a randomized trial in which participants were assigned to levels of any psychological variables, nor did we attempt to manipulate any variables in this study. We cannot provide proof regarding a causal relationship or lack thereof, of any variables. Furthermore, the lack of association between psychological distress and IVF outcomes does not imply that there are no psychological pathways whereby psychological factors could impact IVF success or failure. For example, it is possible that hypothesized neural or hormonal mechanisms might exert an influence in subgroups of patients with certain infertility diagnoses or personality characteristics that this report did not identify. We did not obtain data on the use of psychotherapy or psychopharmacological treatments that may have influenced our findings. Our sample size compares favorably with the existing literature (1–4) but might have been inadequate to detect relatively small effects. The follow-up period is still relatively short (average 2.5 months) and more ongoing research is needed. Also, we do not know if these findings extend to fertility treatments other than IVF.

We concur with Boivin et al (2) that patients should be reassured that the evidence does not suggest that depression and anxiety experienced prior to treatment negatively impacts their chances of succeeding with IVF. This reassurance alone may help to reduce the stress of IVF, as patients may be less likely to blame themselves in the event of failure. Self-blame

for failed IVF can complicate emotional processing after unsuccessful attempts (e.g., “If only I’d been less stressed, I would be pregnant now”) (24). We also concur with Matthiesen (3) that the current literature does not support a general recommendation for psychological interventions to increase IVF pregnancy rates. However these findings do suggest an urgent need to reduce the stress of IVF and to help patients cope with treatment and treatment failure. As argued by Boivin and colleagues, these efforts must be targeted and address multiple domains, including patients factors (e.g., pre-existing psychological distress, as shown in the present study to present high risk for post-IVF distress), as well as clinic and treatment factors (25). Clinic and treatment factors are important so that the burden of stress reduction is not placed solely on the patient, but instead shared by the physicians, nurses, laboratory personnel, billing staff, and pharmaceutical companies. For example, recent research has suggested that perhaps some treatment protocols might be associated with lower distress while maintaining pregnancy rates (26), and that interventions can be targeted to all patients at specific points along the treatment process by specific staff (ie, phones calls from IVF nurses during the waiting period) (27). The development of intervention strategies to reduce stress and improve coping are important not only toward the goal of reducing emotional suffering, but also to reduce the likelihood that patients prematurely drop out of treatment before they reach their ultimate goal of pregnancy (28, 29).

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Table 1

Characteristics of women undergoing their first cycle of IVF

Mean age (SD) (range)	**35.5 (4.5) (range 24–45)**
Annual Household Income (%)	
<$100,000	24%
$100,000–150,000	35.7%
$150,000–200,000	21.9%
>200,000	18.4%
Education	
High school graduate	21%
College graduate	79%
Ethnicity %	
Caucasian	76.9%
Other	23.1%
Parity	
Primary	86%
Secondary	14%
Duration of infertility	
< 1 year	16 %
1–2 years	36.5%
> 2 years	47.5%
Pre IVF depression	12.08 (9.83) (range 0–56) 28% in clinical range
Pre IVF anxiety	41.00 (11.57) (range 20–76) 56% in clinical range
Post IVF depression	14.14 (10.66) (range 0–46) 37% in clinical range
Post IVF anxiety	41.55 (13.25) (range 20–74) 57% in clinical range

n=202 first-time IVF patients.

Means in table, standard deviations in parentheses.

Depression scores from 0–60, risk for clinical depression indicated by scores >=16, anxiety scores from 20–80, risk for clinical anxiety indicated by scores >=39.

Table 2

Mean values for pre-IVF psychological distress by outcome of first IVF cycle

Pre-IVF Distress	IVF success (n=57)	IVF failure (n=145)	P value
Depression	11.29 (8.77) 33% clinical range	12.39 (10.23) 26% clinical range	.48
Anxiety	39.96 (11.67) 55% clinical range	41.41 (11.55) 57% clinical range	.43

Notes. IVF success defined as live birth or confirmed, ongoing pregnancy at the conclusion of investigation. IVF failure defined as IVF cycle start with no pregnancy or with miscarriage.

Means in table, standard deviations in parentheses.

Table 3

Mean values of post-IVF depression and anxiety by treatment outcome

Post-IVF Distress	Pregnant (n=62)	IVF failure (n=103)	In cycle (n=37)
Depression	11.43 (8.22)[a] 30% clinical range	15.85 (11.70)[a] 44% clinical range	14.31 (10.85) 34% clinical range
Anxiety	38.47 (11.68)[b] 50% clinical range	43.33 (14.13) 60% clinical range	42.14 (12.82) 60% clinical range

Note. Means sharing a common superscript significantly differ, $p < .05$.