Psychological stress and infertility

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INTRODUCTION

Psychologic factors such as preconception stress may increase the risk of infertility. In a 12-month, prospective observational study of women starting to attempt pregnancy naturally, salivary alpha-amylase (an index of stress) was measured at baseline [1]. After adjusting for potential confounding factors (eg, age of the woman, consuming alcohol, and smoking cigarettes), the baseline level of alpha-amylase predicted subsequent infertility, such that infertility was more than twice as likely to occur in women with the highest tertile levels of alpha-amylase, compared with women in the lowest tertile.

In addition, there is evidence that stress levels contribute to patients' decisions to discontinue infertility treatment [2,3]. Stress also affects patients' reactions to pregnancy loss during infertility treatment and pregnancy complications.

Many patients with infertility and psychological stress (eg, anxiety and/or depressive symptoms) do not receive mental health services [4].

PREVALENCE OF STRESS

Psychological distress (eg, anxiety and/or depressive symptoms) is common in couples with infertility, and appears to be more common in the partner with the fertility problem [5]:

- A prospective, 18-month study followed women (n = 352) who presented for treatment at an infertility clinic, along with their male partners (n = 274), using self-report instruments to assess clinically significant symptoms of anxiety and/or depression [4]. The primary findings included the following:

  - Anxiety was present at baseline in approximately 50 percent of the women and 33 percent of the men; at one or more assessments, anxiety was present in approximately 75 percent of the women and 60 percent of the men.

  - Depression was present at baseline in approximately 25 percent of the women and 10 percent of the men; at one or more assessments, depression was present in approximately 55 percent of the women and 33 percent of the men.

- In a prospective study of women (n = 112) seeking treatment for infertility, structured interviews with a psychiatrist at baseline found that at least one psychiatric disorder was present in 40 percent [6]. The most common were generalized anxiety disorder (23 percent), unipolar major depression (17 percent), and persistent depressive disorder/dysthymia (10 percent). These figures suggest that psychiatric disorders may be more prevalent among infertility patients than primary care patients and the general population. (See "Unipolar depression in adults: Epidemiology".)

Risk factors for anxiety or depression in infertility patients include a prior history of psychiatric illness, prior history of pregnancy loss, a longer history of infertility, and definitive medical diagnoses for infertility that might lead to poorer prognoses (eg, premature ovarian failure or severe endometriosis). As an example, in one small, prospective, six-month study of women (n = 25) who were undergoing infertility treatment and had a past history of unipolar major depression, relapse of depression occurred in 44 percent (n = 11) [7].

Women with a prior history of depression are at increased risk of experiencing infertility [8]. In addition, women who are depressed are less likely to undergo infertility treatment. One prospective study in new female infertility patients (n = 416) found that 41 percent screened positive for depressive symptoms, and that the depressed women were half as likely to initiate treatment, compared with women who did not score in the depressed range [9].

The stress of infertility has persisted during the coronavirus disease 2019 (COVID-19) pandemic. In an online survey completed in April 2020, females attending an infertility clinic (n >2200) were asked to identify stressors [10]. The two leading stressors were infertility and COVID-19 (66 and 63 percent of patients).

ASSESSMENT OF STRESS

The psychological status of infertility patients should be assessed, ideally through structured interviews with a mental health professional but at a minimum through the use of valid self-report questionnaires [2,11]. In particular, women with a history of anxiety and/or depression should be carefully evaluated prior to commencing infertility treatment.

Investigators have routinely utilized self-report questionnaires to evaluate the stress level of infertility patients. This approach may under-report the true level of distress because patients may feign emotional well-being in order to appear psychologically appropriate for infertility treatment. In research studies, the gold standard in psychological assessment is a structured personal interview with a trained mental health professional (eg, psychiatrist or psychologist).

Clinicians can assess stress by observing patients and inquiring about the patient's emotional state. The main sources of stress for infertility patients include the impact of infertility on their social life, their sexual health, and their relationships with their partner. Thus, we recommend questions about each of these areas, such as:

- Do you feel uncomfortable being around pregnant women and/or children or babies?
- Do you find that you try to avoid situations where there may be pregnant women or babies/small children?
- Is your sexual relationship very satisfying, satisfying, or dissatisfying? If it is dissatisfying, do you feel that your infertility has had a negative impact on your sex life?
- Do you only make love during the fertile times of your cycle?
- Do you feel that you and your partner mostly agree about how to proceed with infertility treatment?
- Do you feel that your partner is sympathetic and supports you?
- How is your mood? How have you been feeling? Are you able to enjoy your usual activities?
- Are you worried? Do you have difficulty concentrating or sleeping? Are you restless?
- Has your appetite changed?

Additional information about assessing patients for anxiety and/or depression is discussed separately. (See "Unipolar depression in adults: Assessment and diagnosis", section on

'Assessment' and "Generalized anxiety disorder in adults: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis", section on 'Screening, assessment, and diagnosis'.)

IN VITRO FERTILIZATION PATIENTS

Overview — The level of stress in infertility patients tends to increase as treatment intensifies and as duration of treatment continues [12]. Therefore, in vitro fertilization (IVF) patients would be expected to experience more stress than women early in their infertility evaluation.

In addition, medications that are used to treat infertility may contribute to depressive symptoms [13]. In a randomized trial that included women taking leuprolide (n = 15), clinically significant depression occurred in 60 percent (n = 9) [14]. Also, an observational study of women taking gonadotropin-releasing hormone agonist medication (n = 16) found that depressive symptoms occurred in 75 percent (n = 12) [15].

Many IVF patients report depressive symptoms prior to beginning their cycle, which likely reflects the impact of repeated, unsuccessful, less invasive forms of treatment, but may also reflect a prior history of mood/anxiety disorders independent of infertility. As an example, one prospective study of 98 women showed that 54 percent of patients reported mild depressive symptoms prior to initiating an IVF cycle and 19 percent had moderate to severe levels [16]. IVF is highly invasive and intensive, and patient distress is common. In addition, most IVF patients state that treatment is more of a psychological than a physical stressor [17]. Nearly half of female IVF patients report that infertility was the most upsetting experience of their lives [18].

Several psychosocial factors are associated with the emotional adjustment of IVF patients. A review of 23 observational studies found that across multiple studies, neuroticism (negative emotional states such as anxiety and depression) and escapist coping strategies (avoidance or distraction) were each risk factors for distress [19]. By contrast, social support was associated with decreased distress.

Most IVF patients report symptoms of depression, anxiety, anger, and isolation after unsuccessful treatment. Many of these symptoms persist over extended periods of time. In one retrospective study of 86 couples who did not conceive with IVF [20], 66 percent of women and 40 percent of men reported symptoms of depression following their failed IVF treatment and one-third of the respondents reported depressive symptoms 18 months later.

Impact of stress on drop-out — Infertility specialists traditionally have assumed that patients drop out of treatment for only two reasons: active censoring (their clinician advises the couple

to terminate treatment due to a poor prognosis) and finances (the procedure is often not covered by insurance). However, this assumption has been challenged; the majority of insurance-covered patients voluntarily terminate treatment prior to completing their allotment of covered cycles and the major reason for drop-out appears to be the psychological burden of the procedures.

Active censoring appears to be less common than previously thought. A study in the Netherlands, where IVF cycles are covered by insurance, showed a cumulative drop-out rate after three cycles of 62 percent, only 14 percent of which was due to active censoring [21]. Most patients gave up because of passive censoring, which the authors defined as giving up treatment because of natural conception or personal reasons.

Research also suggests that cost is frequently not the motive for dropping out; rather, the reason is often stress:

- In one retrospective study of 974 couples in Sweden, 65 percent did not complete the three IVF cycles which were covered under their health plan [22]. The authors speculated that the high attrition rate was due to the physical and emotional burdens associated with IVF, but did not specifically ask couples why they discontinued treatment.

  A similar retrospective study in Australian couples (n = 229) had comparable results [23]. Couples were offered up to six cycles free of charge but the mean number of started cycles was only three, whether or not a live birth was achieved. Among patients who terminated treatment, the most common reasons were emotional (66 percent).

- A prospective study contacted 211 couples who had insurance coverage for IVF, but dropped out for reasons other than active censoring, and asked them for the main reason for their decision [24]. The most commonly cited reason was psychological burden, followed by the perception of poor prognosis. Patients who dropped out of treatment were as satisfied with their treatment as those who did not drop out. These findings were consistent with a similar study in which 515 patients who terminated treatment were contacted and asked to give the reason for their decision [25]. Psychological stress was the most common reason cited, followed by lack of success.

- In a retrospective study of 2130 patients who were covered by insurance for four cycles, the drop-out rate of nonpregnant patients was 40 percent after the first cycle and 62 percent after the fourth [26]. The author hypothesized that the progressively increasing drop-out rate was attributable to the “enormous stress and frustration” during treatment (the patients themselves were not surveyed).

- In a cross-sectional study of 312 insured patients who completed one IVF cycle but did not return for treatment and did not achieve a live birth, 65 percent chose to terminate treatment and did not seek out care elsewhere [27]. The most common reason for dropping out was the psychological burden.

A patient's psychological state may predict dropping out of IVF. As an example, one prospective study administered a battery of psychological questionnaires to new patients prior to starting treatment and found that increased pretreatment levels of depression were associated with patient drop-out after only one cycle [28]. In a subsequent prospective study of 139 couples undergoing infertility treatment, the strongest predictor of treatment termination was the depression level of the female partner (even more so than age) [29].

Although distress levels in female patients undergoing IVF are associated with increased rates of prematurely dropping out of treatment, it is not definitive that treating distress can reduce premature discontinuation of IVF or increase pregnancy rates. (See 'Specific interventions' below.)

Impact of stress on IVF outcome — The impact of psychological distress on the outcome of in vitro fertilization (IVF) is important because most IVF patients report symptoms of anxiety and/or depression prior to commencing IVF treatment, and IVF is by far the most expensive and invasive form of infertility treatment. As discussed elsewhere in this topic, distress is one reason that couples drop out of IVF programs before achieving a pregnancy. (See 'Impact of stress on drop-out' above.)

Research on the impact of distress on IVF outcome is more generalizable than for other infertility treatments because the protocol for IVF is comparable internationally. However, the interpretation of some of this research is limited by methodologic problems, including small sample sizes, measures of distress taken at different stages of treatment, use of different psychological questionnaires, and lack of adjustment for the potential impact of negative feedback. As an example, patients are aware of their ultrasound and laboratory results and understand when a good response has not been achieved. One would expect these patients to report higher levels of emotional distress, but in the absence of baseline data, it is difficult to determine whether the distress level led to poorer outcomes or whether patients who are experiencing a poor response to the medications (and thus have a poor prognosis) simply are reporting the resultant distress.

The impact of stress on IVF outcome is not clear due to mixed findings across studies; some studies suggest stress is associated with poorer outcomes, and other studies have found that stress is comparable in women who become pregnant and those who do not. Nevertheless,

given the unpleasant nature of distress, and that some evidence suggests stress negatively affects outcomes, interventions to reduce stress in patients receiving assisted reproductive technology is reasonable. (See 'Therapeutic interventions' below.)

Among infertile women who are treated with assisted reproductive technology, multiple studies suggest that stress is lower in patients who successfully become pregnant, compared with patients who do not:

- One meta-analysis included 22 prospective studies that followed infertile women (n >4000) who were treated with assisted reproductive technology [30]. Greater levels of pretreatment anxiety and of depression were each associated with statistically significant lower pregnancy rates, but the clinical effect was small.

- A subsequent meta-analysis by the same group included 11 studies with infertile women (n >2200) who were treated with assisted reproductive technology [31]. Anxiety and depression during treatment were each associated with lower pregnancy rates, and the clinical effects were small to moderate.

By contrast, two meta-analyses suggest that stress is not associated with outcomes for patients treated with IVF:

- A meta-analysis included 14 prospective studies that assessed pretreatment stress (anxiety or depression) among infertile women (n >3500) who underwent a single cycle of assisted reproductive technology [32]. The meta-analysis found that pretreatment stress in women who achieved a pregnancy and women who did not was comparable.

- A subsequent meta-analysis of 20 prospective studies included infertile women (n >4300) who were treated with assisted reproductive technology [33]. Anxiety, depression, and perceived stress prior to and during treatment were comparable in women who became pregnant and those who did not.

THERAPEUTIC INTERVENTIONS

Based upon randomized trials in patients with psychological distress and infertility, we suggest psychological interventions for reducing distress.

General principles — For infertility patients who are treated with assisted reproductive technologies such as in vitro fertilization (IVF), we suggest an integrated approach to emotional health that focuses upon reducing the burden of treatment [34,35]. The goal is to make treatment less onerous through interventions aimed at patients, staff, and the treatment itself.

For the patient:

- Screen patients for psychological distress with the SCREENIVF or FertiQOL
- Offer general and/or tailored coping interventions
- Provide referral information, especially for patients at high risk for distress
- Incorporate psychological support as part of the cycle
- Ensure that the partner is involved and supported

For the staff:

- Provide communication training
- Promote shared decision making
- Address situations that are problematic for patients and staff
- Address staff workload issues
- Teach stress management strategies

Infertility treatment:

- Simplify treatment protocols
- Focus on infertility prevention
- Support lifestyle changes
- Add support for patients who do not successfully conceive

The following websites include lists of mental health professionals with experience in diagnosing and treating psychological stress in infertile individuals and couples:

- American Society for Reproductive Medicine
- Resolve: The National Infertility Association

Specific interventions — For psychological stress and infertility, individual and group psychotherapy can reduce negative affect such as anxiety, depression, and infertility-related stress [36,37]. Specific interventions include cognitive-behavioral therapy (CBT), coping skills training, group support, mindfulness, relaxation techniques, and stress-management. However, it is not clear whether these interventions increase conception rates.

Evidence that indicates psychosocial interventions can reduce infertility-related anxiety, depression, and distress includes multiple randomized trials:

- A meta-analysis of 20 trials (n >2100 infertile couples) compared psychological interventions such as CBT or mindfulness with control conditions such as usual care or waiting list [38]. Improvement of anxiety, depression, and distress was greater in patients

who received psychological interventions than controls, and the clinical effect was moderate to large. However, heterogeneity across studies was large.

- A meta-analysis of 14 trials compared psychological interventions such as mindfulness with control conditions in patients with anxiety (n >2500 patients), and found that improvement was superior with psychological interventions [39]. However, the clinical effect was small and heterogeneity across studies was large.

- A meta-analysis of 12 trials compared CBT with control conditions in infertile couples (sample size not reported); in nearly all of the trials, CBT was administered in a group rather than an individual format [40]. Improvement of anxiety was superior with CBT and the clinical effect was large. Improvement of depression was also superior with CBT than control conditions and the clinical effect was moderate to large. However, heterogeneity across studies also appeared large.

For women with psychological stress and infertility, it is not clear whether psychosocial interventions can increase pregnancy rates, due to contradictory results across randomized trials:

- A meta-analysis of six trials (n >800 infertile couples) compared psychological interventions such as CBT or mindfulness with control conditions such as usual care or waiting list, and found that pregnancy occurred in more patients who received psychological interventions than controls (relative risk 1.7, 95% CI 1.2-2.4) [38].

- A meta-analysis of 10 trials compared psychotherapy (eg, CBT) with placebo controls in infertile patients (n >1300) [41]. Pregnancy rates were higher in patients treated with psychotherapy than placebo (relative risk 1.4, 95% CI 1.1-1.9), including patients receiving infertility treatment (relative risk 1.180, 95% CI 1.002-1.400). Patients specifically receiving CBT were twice as likely to become pregnant, compared with controls (relative risk 2.0, 95% CI 1.4-2.8).

- However, a meta-analysis of 11 trials (n >2000 patients) compared psychological interventions such as mindfulness with control conditions, and found that pregnancy rates were comparable in the two groups [39].

The studies of psychosocial interventions and pregnancy rates appear to have included patients receiving assisted reproductive technologies, regardless of baseline levels of stress. The benefit of psychosocial interventions for increasing pregnancy rates in women experiencing infertility may be most apparent in those patients who are also experiencing clinically significant stress at the outset of treatment with assisted reproductive technologies.

One of the most established psychological approaches for managing emotional distress in infertile couples is CBT [42,43]. The content of these programs varies, but each generally includes relaxation techniques, stress-management, coping skills training, and group support. Programs range from 5 to 10 sessions, most include the male partner for at least several of the sessions, and are led by mental health clinicians, nurses, or both. Participants report decreases in all assessed psychological and physical symptoms, including depression, anxiety, hostility, fatigue, headaches, insomnia, and abdominal pain [42]. Approximately 45 percent of patients conceive within six months of program completion.

Other treatments for managing the psychological consequences of infertility include mindfulness based interventions. Information about mindfulness-based cognitive therapy is discussed separately in the context of treating depression. (See "Unipolar major depression: Treatment with mindfulness-based cognitive therapy".)

Psychological interventions that are convenient and low cost may improve outcomes. As an example, a 12-month randomized trial compared a self-administered cognitive coping and relaxation intervention with routine care in patients (n = 161) beginning IVF [44]. The active intervention consisted of an educational leaflet, relaxation techniques, and a set of 10 statements intended to facilitate coping by focusing upon positive thoughts and activities during stressful situations (eg, “Try to do something that makes me feel good”). Although pregnancy rates were comparable for the two groups, discontinuation of IVF occurred in fewer patients who received the active intervention, compared with controls (5 versus 15 percent). In addition, improvement of psychological factors (eg, anxiety and quality of life) was greater with active treatment.

It is unclear why a psychological intervention might have a positive impact on pregnancy rates in infertile women. One possibility is that psychological stress affects biologic functions, such as the immunology of the maternal-fetal interface (see "Immunology of the maternal-fetal interface"). As an example, a randomized trial reported psychological distress and natural killer cell activity both decreased in 37 women who received a five-session mindfulness intervention, whereas no change occurred in those who received routine care [45]. During the one-year follow-up period, conception occurred in more patients who received the intervention than controls (38 versus 14 percent).

The use of antidepressant medication in women who are infertile is controversial [46], and many patients decide to discontinue their antidepressant medications before they try to conceive; this can lead recurrence of depression and complicate what is already a difficult situation. Nevertheless, infertile patients with moderate to severe symptoms of stress that result in anxiety syndromes (eg, generalized anxiety disorder) or depressive syndromes (eg,

unipolar major depression) are candidates for pharmacotherapy. In addition, pharmacotherapy may be indicated for patients with stress that does not respond to psychotherapy. Use of pharmacotherapy should include an evaluation by a psychiatrist who can discuss the risks and benefits of taking medications.

Psychotherapy may be more effective than pharmacotherapy for treating stress in infertile women. One small, eight-week, open-label randomized trial in infertile women (n = 62) with depressive symptoms and sexual dysfunction compared psychosexual psychotherapy with bupropion (150 mg/day); patients with unipolar major depression were excluded [47]. Improvement of depression was greater with psychotherapy than bupropion.

SUMMARY AND RECOMMENDATIONS

- Infertile women often experience significant levels of stress, frequently manifested as symptoms of anxiety and/or depression. (See 'Prevalence of stress' above.)
- Psychological discomfort appears to lead to premature termination of in vitro fertilization (IVF) treatment; however, the impact of stress on IVF outcome is not clear. (See 'In vitro fertilization patients' above.)
- For infertility patients who are treated with assisted reproductive technologies such as IVF, we suggest an integrated approach to emotional health that focuses upon reducing the burden of treatment through interventions aimed at patients (eg, screening patients for psychological distress), staff (eg, shared decision making), and the treatment itself (eg, simplified treatment protocols). (See 'General principles' above.)
- For patients with psychological stress and infertility, we suggest psychological interventions rather than pharmacotherapy, to decrease symptoms of anxiety and depression (**Grade 2C**). Suitable psychological interventions include cognitive-behavioral therapy, as well as coping skills training, group support, mindfulness, relaxation techniques, and stress-management. (See 'Specific interventions' above.)

  However, infertile patients with moderate to severe symptoms of stress that result in anxiety syndromes (eg, generalized anxiety disorders) or depressive syndromes (eg, unipolar major depression) are candidates for pharmacotherapy, but the risks and benefits must be discussed. (See 'Specific interventions' above.)

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