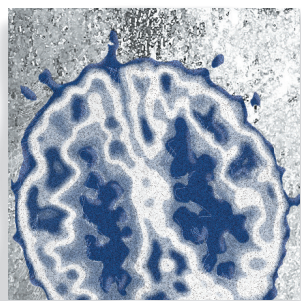


The relationship between stress and infertility

Kristin L. Rooney, BA; Alice D. Domar, PhD



The relationship between stress and infertility has been debated for years. Women with infertility report elevated levels of anxiety and depression, so it is clear that infertility causes stress. What is less clear, however, is whether or not stress causes infertility. The impact of distress on treatment outcome is difficult to investigate for a number of factors, including inaccurate self-report measures and feelings of increased optimism at treatment onset. However, the most recent research has documented the efficacy of psychological interventions in lowering psychological distress as well as being associated with significant increases in pregnancy rates. A cognitive-behavioral group approach may be the most efficient way to achieve both goals. Given the distress levels reported by many infertile women, it is vital to expand the availability of these programs.

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Introduction

Infertility is often a silent struggle. Patients who are struggling to conceive report feelings of depression, anxiety, isolation, and loss of control. Depression levels in patients with infertility have been compared with patients who have been diagnosed with cancer.¹ It is estimated that 1 in 8 couples (or 12% of married women) have trouble getting pregnant or sustaining a pregnancy.² Despite the prevalence of infertility, the majority of infertile women do not share their story with family or friends, thus increasing their psychological vulnerability. The inability to reproduce naturally can cause feelings of shame, guilt, and low self-esteem. These negative feelings may lead to varying degrees of depression, anxiety, distress, and a poor quality of life.

Patients who undergo assisted reproductive treatment (ART) are at significant risk of experiencing psychiatric disorders and it is important to recognize, acknowledge, and assist these patients as they cope with their infertility diagnosis and treatment.

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Selected abbreviations and acronyms

IVF	<i>in vitro fertilization</i>
ICSI	<i>intracytoplasmic sperm injection</i>
ART	<i>assisted reproductive technology</i>
PCOS	<i>polycystic ovarian syndrome</i>
PGS	<i>preimplantation genetic screening</i>
QoL	<i>quality of life</i>
CBT	<i>cognitive behavioral therapy</i>
M/B	<i>mind/body therapy</i>
CCRI	<i>cognitive coping and relaxation intervention</i>
PRCI	<i>positive reappraisal coping intervention</i>

Background

Infertility is a life crisis affecting patients from all around the world. Infertile patients experience a tremendous amount of emotional turmoil as the result of their diagnosis. The risk of depression, anxiety, and distress is high for infertile patients.

It has been hypothesized since biblical times that stress can hamper fertility. This raises one of the most compelling mind/body questions: does infertility cause stress or does stress cause infertility? The answer thus far is not clear; the relationship between distress and infertility may not have a clear cause and effect direction. It is definitive that infertility leads to significant distress and that psychological interventions are likely to be associated with decreases in depression and increases in pregnancy rates. However, the impact of distress on treatment outcome is less definitive.

This article will review the psychiatric disorders associated with infertility treatment and the potential impact of those symptoms on reproductive treatment outcome, as well as the efficacy of psychological interventions on both distress and pregnancy rates.

The psychological impact of infertility: depression, anxiety, and distress

One of the main challenges in assessing the distress levels in women with infertility is the accuracy of self-report measures. It is possible that women “fake good” in order to appear mentally healthier than they are. It is also possible that women feel a sense of hopefulness/increased optimism prior to initiating infertility treatment, which is when most assessments of distress are

collected. Some early studies concluded that infertile women did not report any significant differences in symptoms of anxiety and depression than fertile women. However, a 2004 study³ utilized a structured psychiatric interview. A total of 122 women were interviewed prior to their first infertility clinic visit and the results were striking; 40% of women were diagnosed as having anxiety, depression, or both. Subsequent research has supported these findings. Volgsten and colleagues⁴ reported a 31% prevalence of psychiatric symptoms, the most common of which was major depression. In a large Danish study of 42 000 women⁵ who underwent ART treatment and were screened for depression prior to treatment, 35% screened positive. In another recent study of 174 women undergoing infertility treatment, 39% met the criteria for major depressive disorder.⁶ In one of the largest studies to date,⁷ 352 women and 274 men were assessed in infertility clinics in northern California. It was determined that 56% of the women and 32% of the men reported significant symptoms of depression and 76% of the women and 61% of the men scored reported significant symptoms of anxiety. Not surprisingly, recent research documents that infertility patients consistently report significantly more symptoms of anxiety and depression than fertile individuals.⁸ Finally, in a recent concerning study on suicidality in 106 women with infertility, 9.4% of the women reported having suicidal thoughts or attempts.⁹

A recent literature review on the prevalence of psychological symptoms in infertility concluded that 25% to 60% of infertile individuals report psychiatric symptoms and that their levels of anxiety and depression are significantly higher than in fertile controls.¹⁰

The medications used to treat infertility, including clomiphene, leuprolide, and gonadotropins, are associated with psychological symptoms such as anxiety, depression, and irritability. Thus, when assessing symptoms of women mid-treatment, it is difficult to differentiate between the psychological impact of infertility versus the side effects of the medication. Thus, studies which included measures of these symptoms prior to beginning medication, or after going off it, may be more accurate than those done only on women as they cycle.

The further into treatment a patient goes, the more often they display symptoms of depression and anxiety. Patients with one treatment failure had significantly higher levels of anxiety, and patients with two failures experienced more depression when compared with

those without a history of treatment.¹¹ However, it has also been shown that the more depressed the infertile woman, the less likely she is to start infertility treatment and the more likely she is to drop out after only one cycle.¹² Researchers have also shown that despite a good prognosis and having the finances available to pay for treatment, discontinuation is most often due to psychological reasons.¹³⁻¹⁵

The impact of stress on treatment outcome

One of the most controversial areas in the field of reproductive medicine is the potential impact of psychological factors on pregnancy rates. Although there are a variety of old wives' tales which support the notion that stress hampers reproduction function, this theory has been challenging to confirm. There have been dozens of studies which have investigated the relationship between psychological symptoms prior to and during ART cycles and subsequent pregnancy rates, with conflicting results. Some have shown that the more distressed the women prior to and during treatment, the lower the pregnancy rates,¹⁶⁻¹⁹ while other studies have not.²⁰⁻²¹

There are several possible explanations for these discrepancies. One is that individuals may not accurately report their level of distress when completing psychological questionnaires. Research supports this theory. In a study of fecundity in 339 women in the United Kingdom trying to conceive,²² self-reported symptoms of depression, anxiety, and stress were not significantly associated with time to pregnancy. However, in a similar study on 501 women in the United States, levels of salivary α -amylase, a biomarker of stress, were significantly correlated with time to pregnancy.²³ Women in the highest quartile of α -amylase levels at baseline were twice as likely to subsequently experience infertility. Finally, in a recent study in 135 IVF patients, cortisol was measured through samplings of hair, which measures levels from the prior 3 to 6 months.²⁴ The hair cortisol levels were significantly correlated to pregnancy rates ($P=0.017$). These findings match what most infertility patients believe; that psychological symptoms have a negative impact on fertility.²⁵

Miscarriage

According to the American College of Obstetricians and Gynecologists (ACOG), studies reveal that any-

where from 10% to 25% of all clinically recognized pregnancies will end in miscarriage.²⁶ Pregnancy loss occurs for many reasons, one of the leading being the chromosomal abnormality of the fetus. Patients who experience a pregnancy loss have met the criteria for post-traumatic stress disorder; the majority of women report suffering from anxiety and depression.²⁷

Many patients undergoing ART are taking advantage of a relatively new scientific advancement known as preimplantation genetic screening (PGS). PGS allows scientists to identify chromosomal defects through the biopsy of a blastocyst and thus can allow the transfer of only normal blastocysts. Patients who take advantage of this testing may increase their chance of pregnancy by eliminating the embryos which would likely result in a miscarriage. PGS is gaining in popularity, with some ART centers only transferring one PGS normal blastocyst per cycle.

However, there are disadvantages of this new science for patients: the cost of PGS can add thousands of dollars to an already expensive treatment cycle, some embryos don't survive to their fifth day, which is when the biopsy must be performed, and some patients will find that there are no chromosomally normal blastocysts to transfer, which can be emotionally devastating. In addition, because the blastocyst is biopsied around day 5 of development and it takes up to 2 weeks to get the biopsy results, all blastocysts are frozen after biopsy and if any are later determined to be normal, the patient must wait a minimum of a month before she can undergo a thaw cycle to transfer the biopsied blastocyst. So PGS adds another waiting period. Instead of the wait between transfer and pregnancy test, there are two waits: waiting for the biopsy results, and then waiting between transfer and pregnancy test.

Repeat failure

Some patients will get pregnant quite easily from ART, conceiving on their first cycle. However, that is the exception; for many it may take years, or not happen at all. The cause of infertility is not always clear; it may be an underlying health condition such as polycystic ovarian syndrome (PCOS), endometriosis, or male factor infertility, or the frustrating diagnosis of unexplained infertility. Knowing the root cause of an infertility diagnosis can reduce the burden for patients as they understand why this may be happening to them; while still heart-

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broken, they can place blame on “something.” Patients with unexplained infertility do not know why they cannot get pregnant. They may become obsessed with this diagnosis. In fact, infertile women may display a high prevalence of obsession.²⁸ Changes to lifestyle, such as exercise, diet, caffeine intake, and sleep may be altered as an attempt to reverse the diagnosis. For some, these changes paired with ART treatment may lead to a pregnancy; for others, it sadly may not.

Psychosocial interventions for women with infertility

There have been dozens of studies on the efficacy of psychological interventions on women with infertility, with outcomes including pregnancy rates/live birth rates as well as multiple measures of psychological distress. Unfortunately, the various meta-analyses performed in the past 14 years fail to agree on the results.

Boivin²⁹ included 25 studies in her meta-analysis. The conclusions on efficacy were:

1. Interventions were more impactful on reducing negative affect than interpersonal functioning,
2. There were no significant differences in pregnancy rates,
3. Group interventions which included actual skills acquisition were more effective than counseling ones,
4. Men and women benefitted equally.

Hammerli et al³⁰ included 21 controlled studies in their meta-analysis and concluded that psychological interventions were not associated with any significant changes in psychological status and that non-ART patients experienced significantly higher pregnancy rates. They also concluded that interventions of six or more sessions were more impactful than shorter ones.

Ying et al³¹ only included 20 randomized studies in their systematic review. They concluded that there were methodological issues with the studies which reported significant results for both pregnancy rates and psychological distress and recommended that more rigorous research needs to be conducted, especially on the most stressful time for infertility patients: waiting for the results of the pregnancy test.

Frederiksen et al³² included 39 studies and reported on both pregnancy rates and psychological symptoms. They concluded that there were statistically significant and robust overall effects of psychosocial interventions... “on both pregnancy rates and a variety of dif-

ferent psychological symptoms.” The conclusions also were that effect sizes were greater for women than for men and higher pregnancy rates were associated with greater decreases in anxiety.

Another 2016 systematic analysis, a Cochrane review, also included 39 studies³³ but the authors stated that the quality of the included studies did not warrant any conclusions. Finally, the third 2016 review³⁴ included only 12 studies of which seven were intervention designs. The conclusions based upon these seven studies were that psychological interventions are associated with less psychological distress, higher pregnancy rates, and improved marital satisfaction.

The mind/body program for infertility

It is evident that infertility patients experience distress, depression, anxiety, and decreased quality of life. It is important for infertility providers and counselors to offer assistance to these patients by way of psychological interventions and emotional support.

The Mind/Body Program for Infertility was created and launched in September 1987. Because psychological interventions for infertile patients can improve psychological outcomes and marital relationships³⁴ as well as increase patient retention and improve pregnancy rates,²⁵ it was hypothesized that a research-based clinical program had the potential to accomplish all of these goals. The program has ten sessions, is a group model, and the partners of participants attend three of these sessions. Mind/Body therapy has been proven a successful way to reduce stress and increase pregnancy rates³⁵ and provides patients with skills in cognitive behavior therapy, relaxation training, lifestyle changes, journaling, self-awareness, and social support components.

The Mind/Body program includes two sessions of cognitive behavioral therapy (CBT) which is a form of psychotherapy that emphasizes the important role of thinking in how we feel and what we do. Participants challenge automatic thought patterns, such as “I will never have a baby,” “the infertility is all my fault,” or “my husband is going to leave me for a fertile woman.”

Relaxation techniques have been widely shown to reduce negative emotions in a range of medical patients,³⁶ more specifically, they have been shown to significantly reduce anxiety scores in women undergoing infertility treatment.³⁷ Patients learn a different technique each week, including progressive muscle re-

laxation, hatha yoga, meditation, imagery, etc, and are encouraged to try each one and then practice the one(s) which are most effective for them.

A study of both male and female infertility patients explored the benefit of expressive writing. The authors found that both partners exhibited decreased depressive symptoms.³⁸ Participants in the mind/body program do a journaling exercise during the seventh session of the program and are encouraged to continue if they found it helpful. They also are encouraged to maintain a daily gratitude diary.

Mindfulness is commonly used as a coping strategy for infertility patients and is introduced early in the program. A study of first time IVF patients randomized to a mindfulness-based intervention versus control found that women who attended the intervention revealed a significant increase in mindfulness, self-compassion, meaning-based coping strategies, and most importantly had higher pregnancy rates.³⁹

There have been a number of RCTs on the efficacy of the mind/body program.^{35,37,40} Participants experience significantly lower levels of distress as well as a higher pregnancy rate than the control subjects.

Self-administered interventions

Psychological interventions do not necessarily need to be administered by a clinician; there are self-administered options available as well. A randomized controlled prospective study of 166 first-time IVF patients evaluated the use of a self-administered cognitive coping and relaxation intervention (CCRI). The findings suggested that patients utilizing the CCRI displayed more positive reappraisal coping, improved QoL and reported less anxiety.⁴¹ In addition, the intervention participants had a 67% lower dropout rate than the controls.

The 2-week waiting period between embryo transfer and the pregnancy test has been recognized as a very stressful time during IVF treatment. Another self-administered tool is the Positive Reappraisal Coping Intervention (PRCI). The PCRI encourages a form of coping that helps people take account of positive aspects of stressful situations; a strategy particularly useful for unpredictable and uncontrollable stressors such as the 2-week waiting period.⁴² Research on this tool has found it beneficial to utilize during the 2-week waiting period.⁴³

A recent randomized controlled prospective pilot study included an online version of the mind/body program.⁴⁴ Women who were randomized to the intervention group experienced significant decreases in anxiety and depression and a higher pregnancy rate.

Conclusion

A diagnosis of infertility can be a tremendous burden for patients. The pain and suffering of infertility patients is a major problem. Patients must be counseled and supported as they go through treatment. Although neither the American Society for Reproductive Medicine nor the European Society for Human Reproduction and Embryology have formal requirements for psychological counseling for infertility patients, there is acknowledgement that incorporating psychological interventions into routine practice at ART clinics is beneficial. It has been well documented that infertility causes stress. The impact of stress on ART outcome is still somewhat controversial. However, it is clear that psychological interventions for women with infertility have the potential to decrease anxiety and depression and may well lead to significantly higher pregnancy rates. □

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La relación entre estrés e infertilidad

Por años ha sido debatida la relación entre estrés e infertilidad. En las mujeres con infertilidad se encuentran puntuaciones elevadas de ansiedad y depresión, por lo que está claro que la infertilidad causa estrés. Sin embargo, lo que está menos claro es si el estrés causa o no infertilidad. Por numerosos factores, como las inexactas mediciones de auto-reporte y los sentimientos de aumentado optimismo al comienzo de los tratamientos es difícil investigar el impacto del estrés en el resultado terapéutico. Ahora bien, la investigación más reciente ha documentado la eficacia de las intervenciones psicológicas en la reducción del estrés psicológico, además de asociarse con aumentos significativos en la frecuencia de embarazos. Una aproximación grupal cognitivo conductual puede ser la forma más eficiente para alcanzar ambos objetivos. Es vital expandir la disponibilidad de estos programas, dado los niveles de estrés reportados por muchas mujeres infértiles.

Relation entre stress et infertilité

La relation entre le stress et l'infertilité est débattue depuis des années. Les niveaux d'anxiété et de dépression des femmes infertiles sont élevés, il est donc clair que l'infertilité provoque du stress. Ce qui est néanmoins moins clair c'est de savoir si le stress entraîne, ou pas, de l'infertilité. De nombreux facteurs rendent difficile la recherche sur l'effet de l'anxiété sur les résultats thérapeutiques, comme les auto-mesures imprécises, et les sentiments d'optimisme accru au début du traitement. Cependant, d'après les recherches les plus récentes, la prise en charge psychologique est efficace pour diminuer l'anxiété et elle s'associe aussi à des taux de grossesses significativement augmentés. C'est l'approche cognitivo-comportementale de groupe qui semble la plus efficace pour atteindre ces deux buts. Il est vital d'élargir la disponibilité de ces programmes compte tenu des niveaux d'anxiété rapportés par de nombreuses femmes infertiles.