Chapter 12
Psychosocial Implications of Recurrent Implantation Failure

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Introduction

Infertility has often been described as an emotional roller coaster as intended parents have sought medical treatment to resolve their fertility problems. Concerns that infertility problems are rooted in psychological issues are reflected in the oft-heard advice of "just relax and you'll get pregnant." Historically, psychological theories were developed as models to explain infertility [1]. Sigmund Freud posited a theory of infertility as a consequence of a fear of impregnation. Later on, Berg and Wilson addressed this psychogenic model more broadly, looking at psychopathology as contributing to or causing infertility [2]. Thus the investigation of psychopathology as contributing to or causing infertility has reflected the lay belief that stress or other psychogenic difficulties are implicated in infertility.

In the past several decades, these psychogenic models have been challenged by the increased ability to diagnose the physiological causes for male and female infertility. Scientific methods and diagnostic means have led to a dramatic change in the understanding of infertility as doctors can now identify many of the physical factors that cause infertility. As a result of this shift, psychosocial research began to focus on the relationship between various aspects of psychosocial functioning on overall success rates in infertility treatment. The hope was that if psychosocial functioning was associated with implantation or endometrial development, it would create opportunities to improve pregnancy outcomes. This research has faced the formidable challenge of controlling for the myriad of intervening variables that could

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contribute to findings of significance or non-significance, resulting in a body of contradictory results.

Psychosocial research has since expanded in breadth, with studies seeking to uncover not only potential links between various psychological factors and pregnancy outcomes but also ways in which psychosocial challenges impact the course of infertility treatment, compliance with treatment protocols, and treatment dropout. These links become all the more relevant with repeated implantation failure, as patients undergo multiple cycles of in vitro fertilization (IVF) and must contend with the stress of IVF on a prolonged basis along with the distress of failure.

This chapter will review the research focused on the scope of psychosocial challenges that infertility patients may experience before, during, and following interventions such as IVF, factors that increase an infertile couple's risk for psychosocial difficulties and the potential impact of psychosocial functioning on pregnancy outcomes. Additionally, an overview of researched psychosocial and psychotropic interventions will provide an examination of treatments which can decrease the psychological burden and prevent poor psychosocial outcomes for infertile couples.

Psychosocial Functioning of Infertility Patients

Researchers and clinicians continue to show interest in the psychosocial functioning of infertility patients for a multitude of reasons. Psychosocial functioning encompasses management of stress, attributions of sources of difficulties, and utilization of relationships in dealing with stress. Understanding an individual's level of psychosocial functioning can assist medical teams in determining which psychosocial interventions would be most pertinent and effective at a given time. Additionally, awareness of infertility patients' coping strategies can help clinicians predict which individuals are more likely to discontinue treatment, adjust poorly, display inconsistent compliance to medication or monitoring, and develop contentious relationships with medical staff.

The stress-diathesis model is useful in understanding the course of psychosocial functioning with infertility. Infertility patient undergo enormous emotional, physical, relational, and sometimes spiritual stressors, putting strain on their coping abilities. The core assertion of this model is that individuals are influenced by both stress and diathesis, the former referring to difficult life events and traumatic experiences and the latter referring to genetics, personality traits, or other qualities that are largely fixed during one's lifetime. As the quantity and significance of stressors increase, in combination with genetic predisposition to mental illness, certain personality traits, and prior losses or adverse experiences, one becomes more vulnerable to mental health setbacks [3]. Infertility can present a perfect storm of many stressors which, coupled with certain predispositions, can leave the individual more vulnerable to an emotional or mental health challenge during treatment.

Functioning of Infertility Patients Before and During Treatment

As the stress-diathesis model would assert, pretreatment functioning can influence an infertility patient's coping and psychosocial adjustment as she begins treatment. Her functioning at the commencement of treatment, however, may not reflect how she functioned before her infertility diagnosis or attempts to conceive. Prior to a diagnosis of infertility, a patient may have contended with fertility issues for years [4], and as such her infertility can be seen as a chronic stressor that has already been present for some time [5].

Even in the absence of information on functioning prior to the infertility diagnosis, assessment of infertility patients' functioning as they are about to begin treatment is valuable for a few reasons. First, this information can shed light on what increased vulnerability one may have to developing a psychiatric disorder or other adverse responses during and after interventions. Additionally, an examination of how an infertility patient continues to adjust during and after treatment can assist in well-timed referrals for mental health treatment or referrals for other coping resources.

Prevalence of Psychiatric Disorders Prior to Commencing Medical Interventions

A number of studies have examined pretreatment functioning of infertility patients and its impact on their adjustment throughout and beyond infertility treatment. In their review of 25 years of research, Verhaak et al. [6] found nine studies among those accepted into the review that considered the impact of pretreatment functioning. One area of investigation in these studies was of state anxiety which develops due to stress and threats, in contrast to trait anxiety which reflects ongoing high anxiety that is embedded in one's personality. The levels of state anxiety among the infertility patients differed between studies, which the researchers hypothesized may have been due to cultural differences based on the countries where the various studies were conducted.

The Verhaak review [6] found, perhaps surprisingly, that overall women did not appear to have levels of depression higher than control groups prior to treatment in most studies. They suggested that the lack of elevated rates of depression pretreatment might be indicative of the hopefulness of starting treatment and taking action to solve the problem. However, this finding is contradicted in other research. For example, one study, not included in this review, found that prior to beginning treatment, 33% of infertile Chinese women endorsed depressive symptoms according to the General Health Questionnaire, a self-report measure [7].

Studies included in the review differed in their methodologies, which could help explain the varying prevalence rates of psychiatric disorders or symptoms prior to

beginning interventions [6]. Approaches to determining pretreatment functioning differed between studies included in the review; some studies only looked at anxiety [8, 9], while others looked at both anxiety and depression [10–12]. Researchers were selective regarding the types of psychiatric difficulties they looked for, typically focusing on anxiety and depression and excluding diagnostic categories such as substance abuse and other conditions such as bipolar disorder.

An additional obstacle to determining rates of psychiatric difficulties in infertility patients was addressed by Williams et al. [13]. They determined in their review examining mood disorders among infertility patients that "only a few studies that investigate depressive symptoms in newly diagnosed infertility patients actually use diagnostically valid and reliable criteria for confirming a mood disorder." Many studies employ methodologies which lack a rigorous diagnostic element, limiting the ability to confirm the presence of diagnosable conditions and more details regarding participants' psychosocial functioning.

In fact, only three studies using more diagnostically valid criteria to determine rates of depression in infertility patients before commencing treatment were identified in the review by Williams et al. [13]. However, those studies' results lack consistency [14, 15]. One study did not find a difference between infertility patients and controls on measures of mood disorders, while another study did find a significant difference, with infertility patients scoring higher on a depression scale as compared with healthy controls.

A study conducted in Taiwan also used more in-depth methodology for diagnosis. Their approach encompassed administration of the Mini International Neuropsychiatric Interview and the Hospital Anxiety and Depression Scale by a board-certified psychiatrist, rather than a more general self-report questionnaire [16]. The overall rate of psychiatric disorders among 112 infertile women who were attending a reproductive health clinic prior to beginning treatment was 40.2%. The conditions that comprised the highest proportion were anxiety disorders, followed closely by depressive disorders. The high rate of generalized anxiety disorder (26.2%) found in the Chen study is consistent with the Verhaak [6] review's finding that state anxiety was higher than control groups in most of the studies they examined.

While the studies and reviews detailed above reveal a mixed picture regarding prevalence of pretreatment psychosocial difficulties among infertility patients, taken together they illustrate that the presence of such difficulties in some infertility patients is undeniable. These difficulties have the potential to intensify throughout treatment and impact the course of treatment.

Prevalence of Psychiatric Disorders During Treatment

A number of studies have been conducted to determine how infertility patients manage psychologically during treatment. Swedish couples undergoing IVF were found to exhibit high rates of psychiatric disorders at the onset of one round of IVF

treatment [17]. The researchers administered an initial screening measure followed up by a comprehensive telephone assessment for those who showed psychological distress on the initial screening. Their findings showed that full criteria were met for DSM IV diagnoses in almost 20% of women and over 7% of men, with major depressive disorder being the most common diagnosis, while another 11% of women and 2.9% of men met a subthreshold diagnosis. Similarly, [18], using two standardized depression scales, found 37% of infertile women undergoing treatment had symptoms of depression, as compared to healthy controls, who had about half that rate.

Another study found that both men and women undergoing IVF who met criteria for a psychiatric diagnosis were more likely to report physical symptoms, with women reporting higher rates of "fatigue, headache, nausea and abdominal pain whereas fatigue and insomnia were the physical symptoms most commonly reported by men with a psychiatric diagnosis [17]." This demonstrates the intersecting nature of mind and body, with both reciprocally influencing the other, sometimes in ways that are difficult to disentangle. As such, psychiatric and physical symptoms can manifest in a variety of ways during treatment, impacting treatment compliance and even willingness to continue treatment.

Factors Influencing Psychosocial Adjustment During and Following Treatment

Investigation into the risk factors that may increase the likelihood of an infertility patient developing psychosocial difficulties has important implications for timely mental health interventions. Not surprisingly, there is evidence that infertility patients who have had major depressive disorder (MDD) in their lifetime are at risk for developing MDD during infertility treatment. A 2016 study, and the only one to date to examine this issue, demonstrated that a diagnosis of MDD prior to commencing treatment was found to be the single largest predictor of MDD during infertility treatment, while controlling for other factors such as partner support, and baseline levels of anxiety and depression [19]. It is clear that some symptoms of MDD, such as sad or irritable mood, poor concentration, decreased motivation, disrupted sleep, and decreased energy levels, have the potential to seriously impact the course of infertility treatment for some patients.

Other variables such as age of woman, amount of time dealing with infertility, the diagnosis itself, and number of IVF or intracytoplasm sperm injection (ICSI) treatments may not present as risk factors for the development of psychosocial difficulties [20]. In this same study, which was conducted among patients in the United States, it was demonstrated that demographic factors such as age and years married were not related to infertility patients' experience of stress. Factors that do appear to impact stress included attitudes, number of tests received, and treatment cost [20].

Van den Broeck et al. [21] investigated factors that contribute to the distress experienced by male and female infertility patients. The factors they found that

played a role in exacerbation of distress were those that would also contribute to the development of psychiatric disorders in the general population. More specifically, they identified the personality dimensions of dependency and self-criticism, poor quality of attachment in their spousal relationship, and poor social support, as having greater significance than specific infertility concerns and characteristics related to the infertility experience. They write that "in this way, the infertility-specific concerns and characteristics might only be secondary expressions of basic psychological dimensions."

Volgsten et al. [22] studied a range of demographic variables and risk factors for the development of psychiatric disorders in infertile couples. They concluded that, for the development of a mood disorder, a previous pregnancy and obesity were independent risk factors for women, while unexplained infertility was a risk factor for men. Interestingly, for women, there were no independent risk factors associated with anxiety disorders, and the sample size for men was too small to draw any conclusions. Despite looking at a very broad range of potential risk factors—age, smoking status, native language, socioeconomic status, economic status, and fertility history—none were significantly related to psychiatric diagnosis, with the exception of previous pregnancy. The researchers noted some surprise at the dearth of identified risk factors, as many of the ones they investigated have been identified as risk factors for the development of psychiatric conditions in the general population. With regard to the socioeconomic and economic factors, these infertility patients were receiving free treatment, as Sweden has universal healthcare that covers up to three IVF cycles. In this context, the particular factors related to finances did not impact the development of depressive or anxiety disorders.

Lack of success in giving birth following infertility treatment may present as a risk factor for poor adjustment in the long term. While there is a dearth of longitudinal studies looking at long-term adjustment to failure to conceive after IVF, researchers have found some evidence of increased depressive symptoms in those patients that fail to conceive, while patients who were successful experienced a resolution in psychiatric symptoms [6].

One large Swedish cohort study by Baldur-Felskov et al. [23] looked at rates of psychiatric hospitalization for women following successful versus failed infertility treatment. They found that those who did not give birth were more likely to have been hospitalized for certain mental disorders including alcohol or drug abuse, psychotic disorders, and other diagnoses, in years to come. An obvious limitation of this study is that it only examined hospitalizations, which represent the most severe manifestation of mental illnesses, but even so, it demonstrates a possibility of elevated risk following treatment failure.

Impact of Psychosocial Functioning on Pregnancy Outcomes

Reproductive doctors and patients want to understand how psychosocial functioning may influence pregnancy outcomes. A 2004 study examined hypotheses for ways in which a patient's experience of stress might influence her reproductive

functioning (Cwikel et al.). For example, they reviewed research showing how various neurochemical pathways related to stress intertwine with the function of the gonadal axis, possibly impacting fertility outcomes. Cortisol, a hormone released in response to stress, was demonstrated to not impact pregnancy outcome in IVF in one study they reviewed, but anticipatory cortisol, the cortisol released right before IVF, appeared to have an impact.

Overall, they indicated that while there appear to be some possible links between the ways in which the physiology of stress may interfere with reproductive processes, researchers have not yet identified clear pathways. However, it is not unreasonable to conclude that the experience of stress has an impact on one's physiology in ways that may impact the outcome of fertility treatment. The study posited a theory based on the research that psychological distress (i.e., depression and anxiety) impacts various physiological systems which in turn may decrease the chances of a successful outcome from IVF or other treatments.

Treatment Burden and Dropout

Repeated implantation failure is a significant part of the treatment burden. Research has shown that undergoing multiple cycles of IVF is associated with negative effects such as depression, hopelessness, and stress and has demonstrated that the waiting period post-embryo transfer is perceived as the time of greatest distress for many, if not most, patients [24]. With repeated implantation failure, it is easy to see that the waiting period, referred to on patient Internet discussion groups as the "two weeks waiting," has the potential to become a time of greatest distress.

Does treatment burden or psychopathology lead to treatment dropout? A 2012 meta-analysis reviewed 22 studies that included 21,453 patients from eight countries [24]. The three most frequently cited reasons for treatment dropout among the studies were postponement of treatment, physical and psychological burden, and relationship and personal problems. Reasons varied across stages of treatment although some were stage-specific. Psychological burden was found to be common across treatment stages and found to be the main reason for discontinuation of treatment across all treatment stages.

Interventions for Managing the Burden of Treatment

Screening Tools

Several tools have been developed to screen for patient distress. SCREEN IVF was developed to specifically screen for infertility distress and successfully identified 75% of patients at risk for depression and anxiety [25]. At their pretreatment and again at 3–4 weeks post-pregnancy test, 279 women were administered the SCREEN IVF instrument comprised of 34 items on general and infertility-specific

psychological factors. The purpose of the tool was to give clinicians a way to identify patients in distress or with a vulnerability to emotional distress so that interventions or referrals could be offered.

The Fertility Quality of Life (FertiQoL) questionnaire is the only internationally developed questionnaire which evaluates the quality of life for men and women experiencing infertility [26]. The self-administered questionnaire has 36 items that assess core (24 items) and treatment-related quality of life (QoL) (10 items) and overall life and physical health (2 items); the reliability measures were satisfactory. Overall, it covers four domains: emotional, mind-body, social, and relational. It is currently available for free in 39 languages. FertiQoL is becoming the gold standard for infertility screening, and the relational factor scores are shown to be useful in assessing relationship adjustment to identify patients undergoing ART who are more likely to report poor or good relationship quality [27]. FertiQoL may be a useful tool in measuring and understanding the impact of repeated implantation failure both in individuals and for couples.

To date other measures that have been developed have had local or convenience samples. One of the more widely used instruments, the Fertility Problem Inventory, was developed on primarily Caucasian Canadians who were involved in infertility treatment [28]. Other instruments available have also had other limitations that limit their general utility. None has been developed to look at neither the specific stress of repeated implantation failure nor specifics of treatment such as the waiting period between embryo transfer and pregnancy test.

Pursuit of Mental Health Treatment by Infertility Patients

Although treatment, such as repeated implantation, create many demands and burdens on patients, most women and men experiencing infertility do not seek psychosocial professional support, even those who are showing psychosocial distress. Verhaak et al. [5] found that though over 30% of women undergoing IVF and 10% of men in their study met criteria for at least one psychiatric disorder or subthreshold diagnoses, only about 11% of them participated in counseling at that time. This low rate surprised the researchers, as counseling was offered and available to all participants at the initial appointment. A low rate of mental health treatment was also noted by Chen et al. [16], in which only 6.7% of those with a psychiatric diagnosis had sought psychiatric treatment in the past. This puts patients at risk for an exacerbation of symptoms, poor treatment compliance, potential disruptions in their relationships, as well as overall decline in their quality of life.

Several hypotheses exist as to why, despite endorsement of symptoms, infertility patients do not pursue psychological support in high numbers even when it is offered to them. One reason is that they are so focused on their fertility needs and thus perceive their emotional needs as beyond the scope of treatment. Patients do not necessarily connect their psychological well-being with their ability to comply with medical treatment protocols and ability to function in other domains in their lives.

Some might fear judgment by medical professionals who may deem them incapable of tolerating treatment or, ultimately, handling parenthood. Chen et al. [16] wrote that "the effort to be a good patient, although a proper way to cope with the stress of an assisted reproduction treatment, may prevent participants from revealing psychological distress to their clinicians" (p 5). A theme that emerges from these hypotheses is that of secrecy, one that still shrouds those struggling with infertility. In a sense, then, the secrecy of a couple's emotional struggles due to infertility becomes yet another dimension of their perceived inadequacy and the accompanying shame.

Chen et al. [16] suggest that some patients may lack an awareness of their own emotional functioning and that "it is possible that estimation based on the subjects' self-assessment of whether or not they are depressed may underestimate these psychiatric disorders" (p 5). Patients may view their suffering as "normal" and thus believe there is nothing that can be done to improve their quality of life or coping. This can pose a risk because in the face of deteriorating psychological health, one may begin to make poor decisions and suffer consequences in relationships. Some researchers have suggested that patients do not seek out psychological counseling because they feel they can handle their stress and view that distress asinherent in the infertility process rather than a pathology that needs intervention [29]. A patient may perceive a referral to psychological counseling as a belief on the part of the medical provider that he or she has "failed" to cope adequately, rather than as an opportunity to increase coping strategies while undergoing treatment.

It should not be understated that acknowledging psychological difficulties continues to carry enormous stigma [30]. For some fertility patients, who are already likely carrying the burden of frustration, shame, and grief, acknowledging psychological problems in a direct way to their doctors may prove to be too much for them to bear, particularly when doctors do not directly ask about this domain of their lives. Patients may be concerned that any stigma attached to the need for psychological support has the potential to limit or deny access to infertility treatment.

Uptake of psychological services was found to be most heavily influenced by three factors: comfort level with consulting with a mental health professional, coping resources, and practical concerns about arranging a meeting with a psychologist/counselor [31]. Patients indicated that their distress level needed to exceed their coping resources, such as social support from family and friends, in order to seek out counseling services. In other words, just because many infertility patients experience distress, it may be a small but distinct porportion whose distress levels tax their coping to the point of pursuing counseling.

Boivin et al. [31] cited two models they believed explained the findings of their study looking at low rates of counseling among infertility patients: the hierarchical-compensatory model [32] and the health belief model [33]. The hierarchical-compensatory model proposes that individuals seek out support in a hierarchical fashion, first seeking it from those close to them, then from professionals; this is consistent with the findings in this study, in that participants tended to seek social support first and the majority found it sufficient for their needs and so did not seek out professional support. The health belief model puts forth the hypothesis that individuals determine the extent of their distress that would warrant them seeking

out professional services. In other words, patients may only seek help if they feel their distress is intense enough. The most highly distressed patients in this study tended to cite logistical concerns as a barrier to obtaining treatment, even though services had been offered to them and had been advertised through the clinic where they were being treated.

This introduces questions around why these high-distress patients struggled to obtain the professional support they needed despite it being made available to them. The researchers suggest some possible reasons, such as high levels of distress making it difficult for patients to take in practical information about initiating services [34] and the need in those cases for counseling staff to do more to facilitate the provision of services to those high-distress patients.

Psychosocial Interventions

Myriad behavioral and cognitive interventions for coping with treatment burden have been explored in various studies. Early studies looked at the impact of group psychological interventions [35] and found that group interventions made a significant difference in pregnancy rates, but later studies have not replicated those findings [36]. Further studies looked at mind-body approaches for managing the burden of treatment and found them effective at reducing symptoms of depression and stress and increasing a sense of social support [37] in contrast to the earlier studies which focused on whether interventions increased pregnancy rates.

A recent meta-analysis reviewed 14 different types of interventions that were included in 20 randomized controlled studies [38]. The interventions were classified into five categories: cognitive behavioral therapy (CBT) ($n = 3$), mind-body intervention (MBI) ($n = 3$), counseling ($n = 4$), positive reappraisal coping therapy ($n = 2$), and other psychosocial interventions ($n = 8$) which included hypnosis, Internet-based interventions, crisis interventions, expressive writing, harp therapy, written emotional disclosure, telephone emotional support, and group psychotherapy. The genre of skills taught involved psychoeducation, skill training, emotional support, and cognitive restructuring. This review found that cognitive behavioral therapy, mind-body interventions, counseling, and coping therapy are the most frequently adopted psychological interventions for infertile women and men. However, the review did not find that counseling interventions showed positive effects. The authors recommend that new therapeutic approaches with proven efficacy be the focus to support individuals and couples going through infertility with particular attention to the "two weeks waiting" time prior to the pregnancy test, an area which has been inadequately researched.

Cognitive approaches with positive cognitive reappraisal have been found to lead to modest gains in easing the psychological burden but have not been found to increase pregnancy rates [39]. Patients were randomized into either a control or treatment group prior to the start of their IVF cycle. The treatment group was given a set of ten statements which facilitate positive thinking and diminish dwelling on

negative aspects. Researchers found that the exercise did not diminish treatment dropout or increase pregnancy rates, though it was perceived as helpful.

As patients are getting more information and support online, online interventions have been developed for psychoeducational support [40]. A total of 190 women were randomized into two experimental and two no-treatment control groups. After the e-health module, trends were observed for utility in several psychological domains: decreased global stress ($P = 0.10$), sexual concerns ($P = 0.059$), distress related to child-free living ($P = 0.063$), increased infertility self-efficacy ($P = 0.067$), and decision-making clarity ($P = 0.079$). Easy access to online e-health modules could be adapted for patients experiencing repeated implantation failure. Sub-modules could address managing the specific burden of repeated implantation failure.

Psychotropic Medication Management

A more recent area of investigation is the use of antidepressants or anxiolytics and pregnancy outcome [41]. Although there is an existing and emerging body of literature on pharmacological interventions with pregnant and postpartum women, very few studies have examined the relationship of pharmacological interventions with the infertile population. Estimates are that more than half of women pursuing infertility treatment take antidepressants [42]. In a recent analysis of a Swedish birth registry from 2007 to 2012 of women who went through IVF, researchers found that women who were using antidepressants before IVF were found to have slightly reduced odds of pregnancy and live birth [42]. Women with depression and/or anxiety who were not taking antidepressants had a more pronounced reduction in odds for pregnancy. The analysis was unable to identify or speculate what the mechanism might be for the reduction, e.g., is it the underlying disease impacting on egg or embryo quality, mechanisms for implantation, or some other factor?

Research has explored whether psychotropic medication such as antidepressants is effective in the treatment of depression, and many studies conclude that the efficacy and risk do not warrant their use [43]. However, other reviews have concluded that the use of antidepressants is relatively safe and their use is warranted for both maternal and fetal health [44].

As a result of the controversy around psychotropic medication's efficacy and whether it may decrease chances of success for pregnancy, along with the potential for risks during pregnancy to the developing fetus, there has been a call for a reduction or a cessation of use for infertility patients [45]. Clinicians were urged to refer to known effective treatments for depression and anxiety such as cognitive behavioral therapy which has none of the medication risks. Those researchers who have not concluded that there is a significant risk do endorse using medication during treatment and pregnancy citing that that there are significant risks from the depression that must be taken into consideration.

Reducing treatment burden is argued to enhance infertility treatment care for both patients and providers [46]. Patient distress can impact and contribute to the

stress load for staff which can impact treatment. It is easy to see how additive cycles of implantation failure can be mitigated if staff are aware of and responsive to patient distress.

Conclusion

The literature around the psychosocial impact of infertility and repeated implantation failure is full of inconsistencies and methodological challenges. There is not a clear consensus regarding the role of interventions for coping with the emotional challenges and its impact on treatment outcome. However, research is showing promising strategies for coping with the emotional impact which may help foster resilience, thus allowing patients to remain in treatment to maximize their biological potential. Certainly, repeated implantation can impact expectations and hope which can influence treatment compliance. These promising strategies yield increased quality of life for individuals and couples pursuing treatment. Collaborative care for the infertile patient remains the gold standard for best practices for patient care.

References

1. Boivin J, Gameiro S. Evolution of psychology and counseling in infertility. Fertil Steril. 2015;104(2):251–9.
2. Berg BJ, Wilson JF. Psychological functioning across stages of treatment for infertility. J Behav Med. 1991;14(1):11–26.
3. Ingram RE, Luxton DD. Vulnerability-stress models. In: Development of psychopathology: a vulnerability-stress perspective. Thousand Oaks: Sage; 2005. p. 32–46.
4. Mazure CM, Greenfeld DA. J Assist Reprod Genet. 1989;6:242–56. https://doi.org/10.1007/BF01132873.
5. Verhaak CM, Smeenk JM, Evers AW, van Minnen A, Kremer JA, Kraaimaat FW. Predicting emotional response to unsuccessful fertility treatment: a prospective study. J Behav Med. 2005;28(2):181–90.
6. Verhaak CM, Smeenk JM, Evers AW, Kremer JA, Kraaimaat FW, Braat DD. Women's emotional adjustment to IVF: a systematic review of 25 years of research. Hum Reprod Update. 2007;13(1):27–36.
7. Lok IH, Lee DTS, Cheung LP, Chung WS, Lo WK, Haines CJ. Psychiatric morbidity amongst infertile Chinese women undergoing treatment with assisted reproductive technology and the impact of treatment failure. Gynecol Obstet Investig. 2002;53(4):195–9.
8. Mori E, Nadaoka T, Morioka Y, Saito H. Anxiety of infertile women undergoing IVF-ET: relation to the grief process. Gynecol Obstet Investig. 1997;44(3):157–62.
9. Visser AP, Haan G, Haan G, Wouters I. Psychosocial aspects of in vitro fertilization. J Psychosom Obstet Gynecol. 1994;15(1):35–43.
10. Edelmann RJ, Connolly KJ, Bartlett H. Coping strategies and psychological adjustment of couples presenting for IVF. J Psychosom Res. 1994;38(4):355–64.

11. Hearn MT, Yuzpe AA, Brown SE, Casper RF. Psychological characteristics of in vitro fertilization participants. Am J Obstet Gynecol. 1987;156(2):269–74.
12. Verhaak CM, Smeenk JM, Eugster A, van Minnen A, Kremer JA, Kraaimaat FW. Stress and marital satisfaction among women before and after their first cycle of in vitro fertilization and intracytoplasmic sperm injection. Fertil Steril. 2001;76(3):525–31.
13. 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):607–16.
14. Downey J, Yingling S, McKinney M, Husami N, Jewelewicz R, Maidman J. Mood disorders, psychiatric symptoms, and distress in women presenting for infertility evaluation. Fertil Steril. 1989;52(3):425–32.
15. Fassino S, Piero A, Boggio S, Piccioni V, Garzaro L. Anxiety, depression and anger suppression in infertile couples: a controlled study. Hum Reprod. 2002;17(11):2986–94.
16. Chen TH, Chang SP, Tsai CF, Juang KD. Prevalence of depressive and anxiety disorders in an assisted reproductive technique clinic. Hum Reprod. 2004;19(10):2313–8.
17. Volgsten H, Svanberg AS, Ekselius L, Lundkvist Ö, Poromaa IS. Prevalence of psychiatric disorders in infertile women and men undergoing in vitro fertilization treatment. Hum Reprod. 2008;23(9):2056–63.
18. Domar AD, et al. Psychological improvement in infertile women after behavioral treatment: a replication. Fertil Steril. 1992;58(1):144–7.
19. Holley SR, Pasch LA, Bleil ME, Gregorich S, Katz PK, Adler NE. Prevalence and predictors of major depressive disorder for fertility treatment patients and their partners. Fertil Steril. 2015;103(5):1332–9.
20. Abbey A, Halman LJ, Andrews FM. Psychosocial, treatment, and demographic predictors of the stress associated with infertility. Fertil Steril. 1992;57(1):122–8.
21. Van den Broeck U, D'Hooghe T, Enzlin P, Demyttenaere K. Predictors of psychological distress in patients starting IVF treatment: infertility-specific versus general psychological characteristics. Hum Reprod. 2010;25(6):1471–80.
22. Volgsten H, Svanberg AS, Ekselius L, Lundkvist Ö, Poromaa IS. Risk factors for psychiatric disorders in infertile women and men undergoing in vitro fertilization treatment. Fertil Steril. 2010;93(4):1088–96.
23. Baldur-Felskov B, Kjaer SK, Albieri V, Steding-Jessen M, Kjaer T, Johansen C, Dalton SO, Jensen A. Psychiatric disorders in women with fertility problems: results from a large Danish register-based cohort study. Hum Reprod. 2013;28(3):683–90.
24. Gameiro S, Boivin J, Peronace L, Verhaak CM. Why do patients discontinue fertility treatment? A systematic review of reasons and predictors of discontinuation in fertility treatment. Hum Reprod Update. 2012;18(6):652–69.
25. Verhaak CM, Lintsen AM, Evers AW, Braat DD. Who is at risk of emotional problems and how do you know? Screening of women going for IVF treatment. Hum Reprod. 2010;25(5):1234–40.
26. Boivin J, Takefman J, Braverman A. The fertility quality of life (FertiQoL) tool: development and general psychometric properties. Fertil Steril. 2011a;96(2):409–15.
27. Donarelli Z, Coco GL, Gullo S, Salerno L, Marino A, Sammartano F, Allegra A. The fertility quality of life questionnaire (FertiQoL) relational subscale: psychometric properties and discriminant validity across gender. Hum Reprod. 2016;31:2061.
28. Newton CR, Sherrard W, Glavac I. The Fertility Problem Inventory: measuring perceived infertility-related stress. Fertil Steril. 1999;72(1):54–62.
29. Boivin J. Is there too much emphasis on psychosocial counseling for infertile patients? J Assist Reprod Genet. 1997;14(4):184–6.
30. Parcesepe AM, Cabassa LJ. Public stigma of mental illness in the United States: a systematic literature review. Adm Policy Ment Health Ment Health Serv Res. 2013;40(5):384–99.
31. Boivin J, Scanlan LC, Walker SM. Why are infertile patients not using psychosocial counselling? Hum Reprod. 1999;14(5):1384–91.

32. Cantor MH. Neighbors and friends: an overlooked resource in the informal support system. Res Aging. 1979;1(4):434–63.
33. Rosenstock IM. Why people use health services. Milbank Q. 2005;83(4):Online-only.
34. Suls J, Wan CK. Effects of sensory and procedural information on coping with stressful medical procedures and pain: a meta-analysis. J Consult Clin Psychol. 1989;57(3):372.
35. Domar AD, Clapp D, Slawsby E, Kessel B, Orav J, Freizinger M. The impact of group psychological interventions on distress in infertile women. Health Psychol. 2000;19(6):568.
36. Boivin J, Griffiths E, Venetis CA. Emotional distress in infertile women and failure of assisted reproductive technologies: meta-analysis of prospective psychosocial studies. BMJ. 2011b;342:d223.
37. Psaros C, Kagan L, Shifren JL, Willett J, Jacquart J, Alert MD, Macklin EA, Styer AK, Denninger JW, LaRoche KL, Park ER. Mind–body group treatment for women coping with infertility: a pilot study. J Psychosom Obstet Gynecol. 2015;36(2):75–83.
38. Ying L, Wu LH, Loke AY. The effects of psychosocial interventions on the mental health, pregnancy rates, and marital function of infertile couples undergoing in vitro fertilization: a systematic review. J Assist Reprod Genet. 2016;33:689–701.
39. Domar AD, Gross J, Rooney K, Boivin J. Exploratory randomized trial on the effect of a brief psychological intervention on emotions, quality of life, discontinuation, and pregnancy rates in in vitro fertilization patients. Fertil Steril. 2015;104(2):440–51.
40. Cousineau TM, Green TC, Corsini E, Seibring A, Showstack MT, Applegarth L, Davidson M, Perloe M. Online psychoeducational support for infertile women: a randomized controlled trial. Hum Reprod. 2008;23(3):554–66.
41. Akioyamen LE, Minhas H, Holloway AC, Taylor VH, Akioyamen NO, Sherifali D. Effects of depression pharmacotherapy in fertility treatment on conception, birth, and neonatal health: a systematic review. J Psychosom Res. 2016;84:69–80.
42. Cesta CE, Viktorin A, Olsson H, Johansson V, Sjölander A, Bergh C, Skalkidou A, Nygren KG, Cnattingius S, Iliadou AN. Depression, anxiety, and antidepressant treatment in women: association with in vitro fertilization outcome. Fertil Steril. 2016;105(6):1594–602.
43. Urato AC. Are the SSRI antidepressants safe in pregnancy? Understanding the debate. Int J Risk Saf Med. 2015;27(2):93–9.
44. Kalra S, Born L, Sarkar M, Einarson A. The safety of antidepressant use in pregnancy. Expert Opin Drug Saf. 2005;4(2):273–84.
45. Domar AD, Moragianni VA, Ryley DA, Urato AC. The risks of selective serotonin reuptake inhibitor use in infertile women: a review of the impact on fertility, pregnancy, neonatal health and beyond. Hum Reprod. 2013;28:160.
46. Gameiro S, Boivin J, Domar A. Optimal in vitro fertilization in 2020 should reduce treatment burden and enhance care delivery for patients and staff. Fertil Steril. 2013;100(2):302–9.