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The Elusive Connection Between Stress and Infertility: A Research Review With Clinical Implications

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This article reviews research exploring the interface of stress and infertility, attempting to answer the following questions: Does infertility cause stress? Does stress impact fertility? Does infertility treatment cause stress? Does stress impact treatment outcomes? Can stress reduction effect treatment distress and outcomes? Is there residual stress after treatment? Recommendations are made to mental health professionals to help their infertile patients cope more effectively with infertility stress, and suggestions are offered for future research directions.

Keywords: infertility, stress, IVF, depression, couples

Infertility is a reproductive disease defined by the failure to achieve or sustain a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse. For many, the desire to have children is fundamental, and receiving an infertility diagnosis can be an emotional experience. Infertility affects over 12%, or 7.5 million, American women ages 15–44, or one in six couples. Of these cases, 40% are due to female factors, 40% to male factors, and 20% to a combination or unexplained etiology (Centers for Disease Control & Prevention, 2015).

Infertility presents both a chronic stressor resulting from the threat of loss of plans to have children, and an acute stressor resulting from the infertility treatment itself. Difficulty in conceiving challenges belief systems, trust in one's body, hopes for future parenting, and expectations of one's anticipated adult life. Treatment protocols are invasive, lasting from months to years, and can involve early morning monitoring, appointments at the doctor, daily injections and blood samples, and laparoscopic surgery. The costs are high and failure can occur at any phase. Infertility has been found to create as much emotional distress as having a diagnosis of cancer, heart disease, or HIV (Domar, Zut-

termeister, & Friedman, 1993). Certain phases of treatment are found to be more stressful than others, such as waiting to hear about fertilization, results of the embryo transfer, or an unsuccessful outcome (Demyttenaere, Nijs, Evers-Kiebooms, & Konnickx, 1991). Myriad treatment options make it difficult to know when to stop. Even after a baby is conceived, anxiety often remains (Hjelmstedt, Widström, Wramsby, Matthiesen, & Collins, 2003), as individuals may be conditioned to expect loss. Although often a long-lasting struggle, infertility is not readily understood by others. The stigma associated with it may result in limited sharing with others and isolation.

Two contrasting theoretical models of infertility have respectively considered psychopathology as cause or consequence. Psychodynamically oriented approaches originally posed psychogenic elements, such as a woman's unconscious conflict regarding adulthood, sex, pregnancy, labor, or motherhood, as the cause of infertility (Deutsch, 1945). This has been rejected by most authors, as research has confirmed that biomedical causes (e.g., blocked fallopian tubes, sperm abnormalities, anovulation) account for most fertility problems. The more recent psychological consequences hypothesis proposes that psychological distress is secondary to infertility, citing research on the impact of emotional states and the ability to cope with stress on the neuroendocrinological state of infertile women and men (Demyttenaere, Nijs, Evers-Kieboom, & Konnickx, 1992), and on

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treatment outcomes (Boivin & Takefman, 1995).

For this article, stress is defined as a physiological or psychological response to an external stimulus that exceeds the individual's coping capacity (Lazarus & Folkman, 1984). A review of recent research on how infertility and stress intersect and impact reproductive function is provided.

Does Infertility Cause Stress?

Whereas most infertility patients function within normal limits on measures of depression and anxiety (Verhaak, Smeenk, van Minnen, Kremer, & Kraaimaat, 2005), there can be a substantial subgroup in need of psychological help as they navigate their infertility. Stress can arise as a reaction to the diagnosis, in response to treatment, or be premorbid. Estimates of major depressive disorder and anxiety have ranged from 11% to 39% and 15% to 23%, respectively, among infertile women, and 5% to 15% and 5%, respectively, among men (Volgsten, Svanberg, Ekselius, Lundkvist, & Sunderstrom Poromaa, 2008), surpassing the prevalence rates of the general population and supporting the interconnection between infertility and stress.

In a U.S. probability-based sample of fertile and infertile women, King (2003) found that infertile women as a group, both treatment seekers and nontreatment seekers, had higher anxiety symptoms than fertile women. Infertile women with self-reported depression were less likely to seek medical advice, as well, although this difference was not found for anxiety disorders. Therefore, depression may be a barrier to seeking treatment for infertility. It is important to note that because only approximately half of those experiencing infertility seek infertility treatment (Boivin, Bunting, Collins, & Nygren, 2007), approximately half of the infertile population is omitted when a clinical sample is used in a research paradigm.

Although Gameiro et al. (2016) in a Dutch study found that 63% of women adjusted well to their infertility treatment experience from pre-treatment to 2.5 years posttreatment, 37% showed transient or chronic maladjustment (anxious or depressive) trajectories. Unsuccessful in vitro fertilization (IVF) has been found to be a risk factor for developing depressive symptoms (Verhaak et al., 2005), and can last up to

20 years (Wirtberg, Moller, Hogstrom, Tronstad, & Lalos, 2007). Because women at risk of a maladaptive trajectory can be identified at the start of treatment, that is, reporting marital dissatisfaction, lack of social support, and feelings of helplessness (Gameiro et al., 2016), these psychosocial factors are more amenable to change than demographic or diagnostic variables. As there appears to be an interconnection between infertility and stress, it seems reasonable to provide psychosocial support, both during and after treatment as a preventive approach to infertility care.

Whereas most empirical studies have found that infertile couples report normal levels of marital adjustment relative to presumed fertile couples (Greil, 1997), albeit with some sexual dissatisfaction (Andrews, Abbey, & Halman, 1992), gender differences in response to infertility exist. Women demonstrate stronger emotional reactions earlier in treatment, regardless of whether the infertility is due to female or male factor (Verhaak et al., 2005). Men, however, more generally report more negative emotional responses if the infertility is due to a male factor (Nachtigall, Becker, & Wozny, 1992). Men and women also cope differently. For women, infertility stress often leads to general distress, whereas men's fertility stress remains more contained (Andrews et al., 1992). A man's use of active avoidance coping can increase his female partner's distress, while a woman's use of confronting coping can increase her male partner's distress (Peterson, Pirritano, Christensen, & Schmidt, 2009). Women find relief in processing their thoughts and feelings regarding infertility with others, whereas men find these discussions stressful (Conrad, Schilling, Lagenbuch, Haidt, & Liedtke, 2001). When both members of a couple blame themselves for their infertility, both may experience increases in depression and infertility stress, likely because neither is available to console the other (Peterson, Newton, Rosen, & Skaggs, 2006).

Pasch, Dunkel Schetter, and Christensen (2002) found that if both partners were equally committed to conceiving, and if the man was willing to talk to his female partner about this shared experience, the quality of their communication when discussing infertility was less negative, and women perceived infertility to have a more positive effect on their relationship. Conversely, lack of congruence between dyad

members can add to women's depression and stress.

Does Stress Impact Fertility?

Selye (1950) first suggested an association between stress and infertility, noting ovarian atrophy in rats exposed to stressful stimuli. If stress reduces short-term fertility, it may serve an evolutionary advantage, preventing pregnancy during times when resources are sparse. Chronic stress, however, can result in persistent sexual dysfunction and suppressed fertility.

Research has attempted to delineate the mechanisms contributing to the impact of stress on fertility. Although difficult to isolate single causal links between stress and infertility, associations between stress and the hypothalamic-pituitary-adrenal (HPA) and ovarian axes (HPO) have been found to exist. For example, in response to stress, a cascade of events occur that involve cortisol and epinephrine, resulting in a 'fight-or-flight' response to deal with a threat (Dickerson & Kemeny, 2004). A sustained level of cortisol interferes with the hypothalamus, the region of the brain that produces sex hormones and gonadotropin-releasing hormone (GnRH). It can result in low levels of GnRH, disrupting a woman's ovulatory cycle. Hypothalamic secretion of GnRH stimulates production of luteinizing hormone (LH), causing a follicle to begin to mature and activating the ovary to secrete estradiol and progesterone preparing the lining of the uterus for implantation. Cortisol also increases gonadotropin-inhibiting hormone (GnIH), which inhibits the release of the fertility-enhancing gonadotropins (Chrousos, Torpy, & Gold, 1998). A woman's reproductive system can be completely shut down by functional hypothalamic amenorrhea, and this state increases markedly in proportion to chronic stress (Berga, Daniels, & Giles, 1997).

Lynch, Sundaram, Maisog, Sweeney, and Buck Louis (2014) measured two stress biomarkers during women's attempt to conceive, finding that higher levels of salivary alpha-amylase, but not cortisol, were associated with a longer time to pregnancy and an increased risk of infertility. A recent study measured daily self-reported distress and its relation to the probability of conceiving naturally for up to 20 menstrual cycles among 400 women (Akhter,

Marcus, Kerber, Kong, & Taylor, 2016). Whereas lower pregnancy rates were found with increased self-reported stress during the follicular phase of the menstrual cycle, higher stress during the luteal phase was associated with an increased probability of conception, possibly due to changes in the hormone milieu and/or knowledge of pregnancy.

Stress can affect sperm counts too, as high stress levels have been associated with suppressed libido and significantly lower semen volume and sperm concentration, particularly in chronically stressed men (Tilbrook, Turner, & Clarke, 2000). In severe cases, erectile dysfunction can result in lower frequencies of intercourse and subsequent infertility. Although the role that stress plays in reproductive function has been demonstrated both in animals and humans, whether the degree of stress typically experienced in daily life is significant enough to thwart the reproductive process, naturally or through assisted reproductive technologies, remains equivocal.

Does Infertility Treatment Cause Stress?

Women have reported variability in emotional distress when undergoing infertility treatment (Benyamini, Gozlan, & Kokia, 2005). Even the medications used to stimulate ovarian production and prepare the uterus for implantation can affect mood and contribute to distress (Choi et al., 2005). Mild in vitro fertilization (IVF) treatment (using GnRH antagonist and single embryo transfer) was associated with fewer symptoms of depression one week after treatment failure than standard IVF (GnRH agonist, long-protocol ovarian stimulation, and double embryo transfer; de Klerk et al., 2007). Boivin, Takefman, Tulandi, and Brender (1995) found an inverted U reaction with women who experienced a moderate amount of infertility treatment failure (i.e., intrauterine insemination with an average of 2.17 failed treatment cycles), reporting more personal and couple distress than women who had no prior treatment failure or those with the most treatment failure (i.e., superovulation and IVF with an average of 6.6 failed treatment cycles). The times preceding oocyte retrieval, before and after embryo transfer and while waiting for a pregnancy test, have been found to be particularly stressful (Boivin & Takefman, 1995; Mahajan et al., 2010). The

most consistent finding has been an increase in depression after one or more unsuccessful treatment cycles. Consistent with the gender differences noted earlier, male partners showed no change in anxiety or depression after either successful or unsuccessful fertility treatments (Verhaak et al., 2007).

Women who did not become pregnant with IVF reported higher stress levels during treatment than those who became pregnant (Boivin & Takefman, 1995). However, these women also had a poorer biological response to IVF (e.g., estradiol levels, oocytes retrieved). Thus, the direction of causality could not be determined, as negative feedback during the cycle could have contributed to increased stress. Interestingly, the recall of stress was higher than the women's daily reports of stress during treatment.

The stress of infertility can be further impacted by the coping skills the individual uses. In women undergoing intrauterine insemination, Berghuis and Stanton (2002) similarly found a significant increase in depressive symptoms after receiving negative pregnancy results. Avoidant coping strategies (e.g., avoiding pregnant women) were associated with more distress in response to negative results, whereas active approach-oriented strategies (e.g., problem-focused, positive reinterpretation, support seeking) were associated with better adjustment to negative results.

A cross-sectional study of women attending a fertility clinic in Greece (Gourounti et al., 2012) found avoidant coping was associated with increased stress and state anxiety and a lower perception of personal and treatment controllability. Problem-focused coping was associated with reduced fertility-related stress and depressive symptomatology and a higher perception of treatment controllability. However, women who frequently used emotionally focused coping had higher levels of fertility-related stress. Abbey, Halman, and Andrews (1992) also found that perceived control was associated with reduced stress for both women and men. Verhaak et al. (2005), however, did not find that coping strategies determined adjustment to unsuccessful treatment. As infertility is an uncontrollable stressor, they suggested that active problem-focused coping would be ineffective in reducing stress. Also, they did not find the expected positive relation between avoidant coping and anx-

ety or depression, and hypothesized that avoidance coping may, in fact, be effective when confronting uncontrollable and uncertain stressful situations.

A longitudinal population-based sample of U.S. women compared groups who had or had not received treatment for infertility (Greil, McQuillan, Lowry, & Shreffler, 2011). They found that women having no treatment and no live births reported significantly lower levels of fertility-specific distress than those who received treatment, regardless of whether there was a live birth. Whereas the highest levels of distress were found in women unsuccessful after treatment, distress was reported even among treated women who had a live birth. The researchers concluded that infertility treatment was associated with levels of distress that were higher than those associated with the experience of infertility itself.

Research across a variety of countries has also consistently found that stress affected IVF treatment dropout (Domar, Smith, Conboy, Inannone, & Alper, 2010; Gameiro, Boivin, Peronace, & Verhaak, 2012). Thus, it appears important to identify those patients who are particularly stressed by treatment and provide support to minimize nonmedically advised dropout and the negative consequences of treatment.

Does Stress Impact Treatment Outcomes?

An infertility diagnosis sets in motion an emotional reaction that, if not addressed and treated, may interfere with receiving appropriate medical care and resolution. But does stress impact the result of that treatment? Research findings have been equivocal.

Nationwide European registry-based studies have found that those with a pretreatment diagnosis of depression or anxiety are less likely to undergo IVF and for those who did pursue IVF, it reduced odds of a pregnancy and live birth (Cesta et al., 2016; Sejbaek, Hageman, Pinborg, Hougaard, & Schmidt, 2013). A meta-analysis reported that anxiety, but not depression, was associated with lower clinical pregnancy rates (Matthiesen, Frederiksen, Ingerslev, & Zachariae, 2011). Because depression has been reported to be an obstacle to seeking care for infertility, the rates of depression and anxiety in

cohorts of women undergoing ART may be underestimates.

Facchinetti, Volpe, Matteo, Genazzani, & Artini (1997) found that a greater rise in diastolic blood pressure in response to stressful stimuli predicted a lower likelihood of pregnancy in women about to undergo IVF. More recent studies have begun to assess both self-reported stress and physiological markers of stress during infertility treatment. An, Sun, Li, Zhang, and Ji (2013), in a prospective study of women in China, found that those who became pregnant through IVF had lower levels of cortisol both on the day of oocyte retrieval and the pregnancy test, and lower state anxiety than women who did not experience successful treatment. Women in the Netherlands collected nocturnal urine samples to measure the hormonal concentrations of adrenaline and cortisol at three times (pretreatment, day of oocyte retrieval, day of embryo transfer) during their first IVF/ICSI cycle (Smeenk et al., 2005). These researchers found no significant differences in hormone levels at pretreatment, but women who were successful in achieving pregnancy had lower concentrations of adrenaline at oocyte retrieval and at the time of embryo transfer, and lower self-reported anxiety and depression than unsuccessful women.

Turner et al. (2013) reported that anxiety and perceived stress were significantly higher, and self-efficacy lower, on the day prior to oocyte retrieval and while awaiting a pregnancy test in women failing to conceive with IVF whether first timers or repeat patients. A study controlling for covariates known to be linked to IVF success (e.g., age, BMI, smoking, number of oocytes retrieved and fertilized) assessed both salivary cortisol levels, which measure acute stress, and hair follicle cortisol, which measures cumulative levels of the hormone, over three to six months. They found that whereas there was no relation between acute salivary cortisol and IVF outcomes, higher levels of chronic cortisol as measured in hair was associated with a significantly (27%) lower probability of IVF pregnancy (Massey et al., 2016). However, causal relations cannot be determined by these studies, nor can the results be generalized to untreated populations.

Many studies have also shown the opposite results. Although 46% of their sample was found to be stressed, Nouri et al. (2011) found

no relation between salivary cortisol, subjective stress, or number of oocytes retrieved. Similarly, Butts et al. (2014) found no association between urinary cortisol on the day of oocyte retrieval and IVF outcomes. A large multicenter study in the Netherlands found no effect of anxiety or depression on either cycle cancellation or pregnancy rates for women undergoing their first IVF/ICSI (Lintsen, Verhaak, Eijkemans, Smeenk, & Braat, 2009). A meta-analysis of 14 studies also found no association between pretreatment anxiety or depression in women and pregnancy after an ART cycle (Boivin, Griffiths, & Venetis, 2011). Similarly, a prospective controlled study compared first-timers and those with prior IVF failure (Costantini-Ferrando Joseph-Sohan, Grill, Rauch, & Spandorfer, 2016). They found that neither self-reported measures nor biological markers of stress had any association to IVF outcome. Interestingly, cortisol levels dropped significantly at the time of oocyte retrieval and embryo transfer despite a rise in reported stress, but these hormone levels rose again at the time of pregnancy testing. Those with repeated IVF failures reported the greatest degree of psychological distress, suggesting they may benefit from additional psychological support during and after treatment cycles.

There are many potential reasons for these contradictory research findings, for example, heterogeneity in study designs and whether patients were experiencing a first failure or multiple failure. In most studies, the etiology of the infertility was not specified. If a woman has implicit knowledge of a poor chance of treatment success (e.g., from medical feedback during treatment or her particular profile), she may report more stress at the start of treatment creating a spurious relationship between stress and treatment failure. In addition, infertility patients may respond in socially desirable ways regarding stress, to ensure acceptance for treatment.

Ultimately, the relation between distress and IVF outcomes is likely highly complex and results may well depend on when distress is assessed. Although it is assumed that IVF treatment can bypass the negative biological effect of stress, depression, or anxiety on ovulation with ovarian stimulation procedures, convincing evidence to support this is currently lacking. If participants are responding less well during a cycle, awareness of this poorer prognosis is

likely to affect their emotional state. For a true test of the influence of stress on treatment outcome, patients would need to be blinded to their progress during the cycle. This, however, would create potential ethical issues related to autonomy and informed consent for decisions to continue, cancel, or convert a cycle to an intrauterine insemination.

Does Stress Reduction Impact Treatment Distress and Outcome?

Contemporary high-technological medical care, available to infertile patients over close to four decades, is unmatched by psychological services offered and utilized by this population (Pasch et al., 2016). Indicators of high stress for individuals undergoing infertility treatment suggest the importance of investigating stress reduction modalities throughout treatment cycles to support patients. This is particularly important, as these psychological variables, unlike age and other immutable variables, may be sensitive to interventions that may increase the chance of reduced distress and improved treatment experiences.

Domar and her colleagues conducted some of the earliest stress-targeted psychosocial group intervention studies for infertile women. A randomized controlled prospective study of 184 women starting an IVF cycle after trying to conceive between one and two years, assigned women to either a 10-session Mind-Body group (including relaxation training, cognitive restructuring, exercise and nutrition), a standard support group, or routine care. Pregnancy rates for the three groups were 55%, 54%, and 20%, respectively (Domar et al., 2000). No significant difference was found between the two intervention groups. High dropout rates [60%] in the routine care control group negated unbiased comparisons with this group, although the low pregnancy rate does suggest its ineffectiveness. In another study, Domar et al. (2011) found participation in the Mind-Body group was associated with a 52% pregnancy rate versus 20% in a no-treatment control. However, only 76% had completed at least half of the sessions before beginning their second IVF cycle, demonstrating the difficulty in having patients postpone treatment even when attempting to increase their chance of success.

Four meta-analyses have assessed the effects of psychosocial interventions on both psychological distress and clinical pregnancy rates. In the earliest, Boivin (2003) found that psychotherapeutic interventions were associated with a reduction in negative affect in women and couples undergoing infertility treatment. Group interventions emphasizing psychoeducation and skills training (e.g., relaxation training) were significantly more effective in reducing depression, anxiety, and fertility-specific stress than interventions emphasizing emotional expression and/or support, but had little influence on pregnancy rates. Boivin concluded that the distress reduction did not have a sufficiently large impact to overcome biological mechanisms interfering with pregnancy. A subsequent meta-analysis of 22 studies (de Liz & Strauss, 2005) concluded that both group and individual/couples psychotherapy resulted in decreases in anxiety for patients undergoing fertility treatment. Reductions in depression were greater six months after treatment, but pregnancy rates were not definitively enhanced.

In contrast, Hammerli, Knoj, and Barth (2009) evaluated 21 exclusively controlled studies, both randomized and nonrandomized, and found a positive impact of psychosocial interventions on pregnancy rates, albeit only for couples not receiving IVF, but no significant effect on mental health. A potential publication bias was noted, however, as smaller studies that did not demonstrate efficacy may not have been published. Also, a trend toward higher effects on pregnancy rates was found in nonrandomized versus randomized studies, with no clear explanation provided.

In the most recent meta-analysis including 39 studies, a significant effect of psychosocial interventions on both psychological distress and clinical pregnancy rates among couples undergoing infertility treatment was found, although no statistically significant effects of the interventions were found on infertility stress, marital functioning, or depressive symptoms (Frederiksen, Farver-Vestergaard, Skovgard, Ingerslev, & Zacharie, 2015). No differences emerged between CBT or mind-body interventions (MBI), but group interventions demonstrated better results than online, individual, or couple interventions. Conversely, a systematic review of 20 randomized controlled psychosocial intervention studies found none were effective in reduc-

ing depression or stress for either individuals or couples undergoing IVF treatment, although none measured stress levels during the high stress 2-week wait for pregnancy results, and 80% found no impact on pregnancy rates (Ying, Wu, & Loke, 2016).

Briefer psychosocial interventions have been developed in an attempt to make them more attractive to patients. Domar, Gross, Rooney, and Boivin (2015) mailed stress management packets to participants' homes and found lower rates of psychological stress and reduced treatment termination for women undergoing IVF. Lancaster and Boivin (2008), targeting the 2-week waiting period between embryo transfer and pregnancy results, randomized women to either recommended twice-daily reading of 10 statements of a Positive Reappraisal Coping Intervention (PRCI; e.g., *During this experience I will try to do something that made me feel positive*) or 10 statements of positive self-affirmations (e.g., *During this experience I feel that I am a great person*). Women reported that the PRCI was more helpful in increasing positive feelings, minimizing the strain of waiting, and allowing them to better sustain coping efforts.

Online psychosocial support has also been investigated. In one study (Cousineau et al., 2008), women seeking medical treatment were randomly assigned to online support or no online support. Online support consisted of a MBI/CBT program adapted from the Domar et al. (2000) protocol. Women undergoing online support reported less infertility distress and felt more informed regarding medical decisions. Those spending more than 60 min online with the program demonstrated greater reductions in global stress and increased self-efficacy. The program appeared more beneficial for those women using escape-avoidance coping, but resulted in higher infertility distress in women using distancing to cope, possibly because it forced them to face issues they had been avoiding. A pilot RCT comparing the 10-session Mind/Body Program in an online format to a wait list control found that the intervention group demonstrated significantly lower depression, lower anxiety for those with elevated anxiety at baseline, and a 42% self-reported pregnancy rate compared to 17% for the control group (Clifton et al., 2016).

In conclusion, the impact of psychosocial interventions on anxiety, depression, fertility-related stress, and pregnancy rates during infertility treatment appears to be inconsistent. The effects of psychosocial interventions may be difficult to prove for a variety of reasons: variability in methodological rigor; difficulty finding appropriate control groups; high drop-out rates; prior patient awareness of their prognosis; medications being used overriding any impact of stress; possible subject selection and recall bias; and potential social desirability response bias. Assuming that there exists a negative impact of stress on reproductive outcome, but without clear evidence, has the potential to blame the victim and add additional guilt and frustration to an already burdened population. Determining who may benefit from psychosocial intervention to reduce treatment distress may be of value. Clinical judgment of individuals/couples in need of psychological intervention in coping with infertility treatment can be applied, but should not insinuate that stress is causing the infertility or will reduce chances of pregnancy. This is clearly an issue in need of further research.

Is There Residual Stress After Treatment?

Does infertility-related stress continue to impact women and their spouses after treatment conclusion? Not surprisingly, infertile women who became parents experience greater global well-being than infertile women who did not conceive. Those remaining childfree when evaluated up to 3 years posttreatment still experienced depression, distress, and grief (McQuillan, Greil, White, & Jacob, 2000). Both personal and couple distress decreased for women and men 5 years following unsuccessful IVF (Peterson et al., 2009). Sydsjö, Skoog-Svanberg, Lampic, and Jablonske (2011) found positive relationships among couples 20 years post unsuccessful treatment, although most had added a child to their family. For those who never added a child, women report increased distress when their peers become grandparents (Wirtberg et al., 2007).

During pregnancy, women and men conceiving through IVF exhibit less ambivalence about parenthood and greater anxiety regarding losing the pregnancy than couples conceiving spontaneously (Hjelmstedt, Wid-

ström, Wramsby, & Collins, 2004). In a review, Monti et al. (2015) found no increase in postpartum depression risk among women using ART to conceive. The number of previous ART cycles was predictive of postpartum blues, however, and mothers of multiples were at an elevated risk.

The transition to parenthood is stressful for most new parents. Infertile couples becoming parents reported diminished couple well-being, including a lower intimacy quality of life (QOL) and less frequent sexual intercourse than infertile childfree couples, as did presumed fertile parents (Abbey et al., 1992). A review of 28 studies found consistent evidence that couple satisfaction, emotional well-being, attachment to the fetus, general anxiety, and the eventual parent-child relationship was similar between ART-conceiving and naturally conceiving parents. However, pregnancy-specific anxiety regarding fetal health and survival was elevated in ART women, especially among those who had prolonged treatment failure and higher infertility-related stress. Mothers of multiples consistently had higher rates of anxiety and depression during pregnancy and higher levels of adjustment difficulties after the pregnancy than singleton ART and spontaneously conceiving mothers (Hammarberg, Fisher, & Wynter, 2008).

A series of studies compared parents through IVF and donor insemination to those naturally conceiving or adopting children. They found the quality of parenting, the children's relationship with their parents, and the offsprings' emotional and behavioral adjustment from ages four to adolescence in ART families were all similar or superior to those of families with a spontaneously conceived or adopted child. A small percentage of ART mothers and fathers, however, were found to be overly involved with their children (Golombok, Cook, Bish, & Murray, 1995; Golombok et al., 2002).

In summary, whereas the body of evidence on the issue of residual stress after infertility treatment is still emergent, no major detrimental impact on pregnancy nor parenting has been found. Those who reported higher levels of infertility distress were more anxious about losing the pregnancy, however, than those with less reported infertility-related distress, suggesting a potential benefit to them of support during pregnancy.

Implications for Research

The causal impact of psychosocial interventions may be difficult to prove for many reasons. Most patients do not avail themselves of in-person psychosocial support, either not perceiving themselves in need or rejecting it for practical reasons. This suggests that new and alternative methods of psychological support may need to be developed that prove effective, feasible, and accessible (Boivin, Scanlan, & Walker, 1999).

Future research on the interface of stress and infertility should include use of rigorous research designs (e.g., RCTs), that can allow one to attribute change to the psychosocial treatment itself and ensure reproducibility; determine appropriate control groups and reduce dropout rates, especially in control groups; recruit understudied portions of the infertile population (e.g., men, people of color); utilize multicenter studies to enhance generalizability; create interventions in which patients are interested in availing themselves; and determine what IVF programs can do to effectively lower the stress of infertility treatment itself.

Conclusions and Clinical Guidelines

Despite years of research, the relation between stress and infertility remains elusive. Although stress has been shown in basic animal and human research to impact the reproductive system, stress and fertility do not fall into a simple causal association, and the exact mechanisms by which stress interferes with the hypothalamic-pituitary-gonadal axis is still not clearly understood. The most prudent conclusion would seem to be that stress can disrupt fertility, and although it can cause animals to shut down reproductive function in times under stress, it would seem rarely to permanently obviate conception in humans. Indeed, women have conceived during wars and famine. Nevertheless, distress appears to be a primary reason for patients abandoning fertility treatment prematurely (Domar et al., 2010) and can also cause individuals to indulge in other fertility harming habits (e.g., smoking) or avoid sex with their partner.

Evidence that psychological stress during treatment is associated with negative IVF outcomes is suggestive, but has insufficient causal

proof. A patient's advance awareness of her age-related prognosis make it difficult to prove that psychotherapy alone impacts her treatment trajectory. The medications used in IVF also appear powerful enough to override the effect of stress on the body. Due to the level of distress patients express, however, offering support may be beneficial during this difficult life experience. Longstanding concern that stressors during pregnancy adversely affect fetal and infant well-being also reinforce this recommendation (Dunkel Schetter & Tanner, 2012). Because most infertility patients and their partners are not referred to mental health professionals (Pasch et al., 2016), psychosocial services may need to be more synergistically integrated into infertility care, with periodic screening of the psychological distress that patients are experiencing. At the same time, they need to be ensured that this will not result in treatment refusal, only treatment support. A normalizing and accepting attitude on the part of the medical treatment team, with suggestions of the potential usefulness of psychological support while patients traverse their family building journey, may be more conducive to patients acknowledging their level of stress.

Providing the space for patients to express their feelings about their infertility is essential. The medical goal of overcoming infertility and the psychological goal of supporting one's participation in life even while coping with infertility can complement each other, as patients find themselves caught in a maelstrom of distress during treatment that can feel overwhelming. Working psychotherapeutically with patients experiencing infertility requires sensitivity and attunement to the individual's and couple's emotions and coping skills, as well as medical knowledge. Offering such interventions reflects understanding the complexity of the infertility patient, a desire to help patients reduce their distress and improve their quality of life, and communicates the idea that infertility can set one on a journey, although stressful, that has the power to be transforming. With a strengthened sense of self, infertility can lose its dominance over the patient's life and allow for life to be fully appreciated once more.

As mental health professionals, we are likely to find people struggling with infertility in our practices. Suggestions to help include:

- Manage expectations. Normalize stress and loss of sexual spontaneity as an expected outcome of infertility. Help patients regain a sense of control, feeling prepared for both the medical and emotional process they will face, including preparation for emotional reactions to unsuccessful treatment.
- View infertility as a shared problem. Encourage open communication between members of the couple, as well as time-out from discussing infertility to allow for restoration and resilience-building. Help clients seek outside support to avoid overtaxing the primary relationship.
- Identify women and men who are likely to experience emotional difficulties while experiencing infertility (e.g., lack of couple or social support; prior IVF failure) and offer effective psychosocial interventions.
- Help support patients in their attempts to accept treatment failure, make decisions regarding continuing or terminating treatment, explore alternative means of family building, or adjust to a childfree life. Help expand patients' identities beyond fertility. Help them find ways to receive support and provide for their self-care.
- Give concrete suggestions for handling the stresses prior to, during, and after treatment. Offer information about community resources for emotional support to help reduce isolation.
- Encourage medical programs to decrease patient stress by offering information about the medical, emotional, and financial aspects of treatment; include both members of a couple in treatment; encourage open communication with staff; support single embryo transfer; and provide general psychosocial sensitivity in daily patient care, as well as follow-up care after unsuccessful treatment cycles.

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