Journal of Assisted Reproduction and Genetics (2018) 35:1371–1376
https://doi.org/10.1007/s10815-018-1222-5

OPINION

Case-based care for pre-existing or new-onset mood disorders in patients undergoing infertility therapy

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Received: 13 February 2018 / Accepted: 22 May 2018 / Published online: 2 June 2018

Abstract

The inability to conceive is an immensely stressful event in a woman's life. Thus, it is no surprise that women with infertility have twice the rates of depressive symptoms as women without infertility. Incidence of depression in the general female population is approximately 20% compared to almost 40% in infertile females. Based on this information, we expect many individuals with infertility to have pre-existing mood disorders requiring ongoing treatment. In addition, we expect a subset of women to develop a mood disorder during infertility treatment due to related stressors. The reproductive endocrinology team must understand the impact of stress on pregnancy outcomes, the types of treatment options, and the safety and use of various medications. The goal of this case-based commentary is to summarize information on the relationship between stress and infertility and to offer a guide for a range of treatment options that include non-pharmacologic and pharmacologic therapies.

Keywords Antidepressants · Anxiety · Depression · Infertility · Therapy

Introduction

Infertility can induce high levels of distress that include feelings of depression, anxiety, irritability, guilt, embarrassment, and social isolation. The reproductive endocrinologist must be able to recognize and address mood disorders like depression and anxiety, which may be pre-existing or arise during treatments. The purpose of this commentary is twofold. We will summarize the implications of untreated mood disorders during infertility treatment. We will also discuss psychologic and pharmacologic interventions that may improve a woman's experience with infertility treatments, which may increase pregnancy rates. This commentary presents two clinical scenarios involving patients with mood disorders related to infertility. We discuss below the related impact on fertility outcomes and offer recommendations based on current medical evidence.

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Scenario 1

Patient 1 is 37 years old and previously underwent a tubal sterilization procedure. She presents with her new partner for desired in vitro fertilization (IVF). She was diagnosed with depression in the past and currently has bupropion prescribed. She is stable but wants to know if this medication is safe during IVF and, if not, what she should do next. She also wants to know about other non-pharmacologic options for stress reduction.

Scenario 2

Patient 2 is a 27-year-old, single female who presents to the clinic desiring to use donor sperm to achieve a pregnancy. Despite months of treatment and additional attempted therapies, she does not conceive. She has become increasingly distressed and is concerned about symptoms that include decreased sleep, difficulty concentrating at work, lack of interest in hobbies, decreased appetite, and inability to cope with daily life. She has no prior history of anxiety or depression and requests help with her symptoms.

Mood disorders during infertility

Mental health disorders are common in the general population, so it is no surprise that in 2004, a study found that 40.2% of women starting a new assisted reproduction treatment met criteria for a psychiatric disorder [1]. Researchers also found that the most common diagnosis was generalized anxiety disorder followed by major depressive disorder and dysthymic disorder. The latter disorder was recently changed to persistent depressive disorder in the DSM-V (2013). Domar et al. [2] found similar rates of anxiety and depression with 37% of infertile women meeting the criteria for depression, which was double the control group's rate. A separate study in 2008 found 30% of infertility patients met the criteria for depressive and anxiety disorders, but only the rate of depressive disorders was higher than the general population's [3]. Newton et al. [4] observed that depressive and anxiety symptom rates increased from 11.6 to 25.4% and 10.6 to 14.2%, respectively, after a failed IVF treatment. In a study by Lok et al. [5], depressive symptoms similarly increased from 33 to 43% in female patients prior to IVF and following IVF, respectively. Not surprisingly, several studies have demonstrated that the majority of infertility patients with depression and anxiety were underdiagnosed and untreated [3, 6, 7]. Additionally, only a small proportion of those actually identified with a psychiatric disorder receive ongoing treatment.

Domar et al. [8] found that the most common reason for termination of infertility treatment was stress. They had reported that the two main causes of stress were the strain on a couple's relationship and the unwillingness to continue treatment due to depression or anxiety. Stress has been implicated in decreased fecundity through several hypotheses. Some researchers believe the interaction between stress hormones, the HPA axis, and hormones like GnRH, prolactin, LH, and FSH directly influences fertility [9]. Glucocorticoids exert additional indirect action on the ovaries via a variety of metabolic and growth factors, including IGF-1; direct action via glucocorticoid receptors in ovarian tissue has also been identified [10]. Another interference in reproduction could be that similar neurotransmitters and nuclei within the hypothalamus control both stress and reproduction. Finally, catecholamines, which are found in the female reproductive tract and released in times of stress, can affect fertility by interfering with the transport of gametes through the fallopian tube or by altering uterine blood flow [11]. However, one small prospective study observed that while reported stress was reduced during patients' month of conception as compared to infertile months, there was no difference in urinary excretion of epinephrine, norepinephrine, and cortisol [12]. Thus, the exact relationship between stress hormones and infertility has not been clearly established.

Although research is limited in this topic, there are some studies that address fertility outcomes in women undergoing infertility treatments who have symptoms of depression and anxiety. Ebbesen et al. [13] found no significant difference in perceived stress or depressive symptoms between patients who conceived or did not conceive after IVF. However, they concluded that an increased number of negative life events indicative of chronic stress may be related to decreased likelihood of successful IVF treatment, which may be due to a reduction in the number of oocytes retrieved.

There is limited research addressing fertility outcomes in women diagnosed with mood disorders [14]. Furthermore, the available data is inconclusive as to whether decreasing stress or depressive symptoms increases pregnancy rates. Jonsson [15] identified that patients with a history of prior hospitalization for an affective disorder experienced a 71.2% decrease of expected fertility. However, Odegard [16] concluded that patients hospitalized for unipolar depression or bipolar disorder experienced no different fertility outcomes from the general population. Harlow et al. [17] found that patients with a history of a major depressive episode experience decreased fertility due to earlier than expected reduction of ovarian function.

Regarding fecundity, Nillni et al. [18] found that while former psychiatric medication use increased fecundity, primarily represented by former selective serotonin reuptake inhibitor (SSRI) use, current use of SSRIs, benzodiazepines, or other psychiatric medications while attempting to conceive, did not significantly impact outcomes. Ramezanzadeh et al. [19] found a significant difference in pregnancy rates between the intervention group who received pharmacologic and psychotherapeutic intervention compared to the control group. Domar et al. [20] did not find an increase in pregnancy rate after a brief intervention, but they did note an improvement in psychological status.

An additional important outcome of fertility treatment was the discontinuation of therapy. While there are many reasons why a patient may opt to discontinue fertility treatments, the impact of psychological factors should not be understated. Pedro et al. [21] developed a model attempting to explain a discontinuation rate of 29.5% in their prospective study, and they found that female depression was the strongest predictor.

When caring for women with significant depression and anxiety, it is important to optimize all aspects of health so that patients have the highest chance of achieving pregnancy. Optimization of psychiatric health should be as important as the optimization of weight, hypertension, thyroid disorder, and all other medical illness that can affect fertility and pregnancy.

Treatment interventions

Both depression and anxiety can be treated with psychotherapeutic intervention, psychopharmacologic intervention, or a combination of both. It is important not to exclude complimentary modes of treatment, which include acupuncture, mind-body intervention, and other forms of bodywork.

Non-pharmacologic interventions

The first-line option for treatment of mild depression in infertility patients should be psychotherapy. There are several modes of therapy that can be utilized to treat infertile patients with depression or anxiety, such as interpersonal therapy, couple's therapy, and cognitive-behavioral therapy (CBT). A meta-analysis by Frederiksen et al. [22] showed that psychological interventions, CBT in particular, were effective in reducing anxiety and depression. Additionally, women who received a psychological intervention were twice as likely to become pregnant as compared to controls. Furthermore, an analysis of studies that included outcomes for both pregnancy and anxiety showed that patients with larger reductions in anxiety had greater pregnancy rates. Their findings also suggested that group interventions were more effective than both individual and couple interventions. A study by Facchinetti et al. [23] found that CBT was able to reduce the cardiovascular and neuroendocrine stress response, decreasing the elevated blood pressure, heart rate, and cortisol levels caused by mental stress in infertility patients.

Other complementary or alternative medicine treatments have been shown to be effective as well. Complementary or alternative medicine is used by a minority of patients presenting for infertility treatment. Smith et al. [24] showed acupuncture and herbal therapy were the most commonly used modalities with other forms of bodywork and meditation representing a smaller fraction. Numerous randomized control trials have assessed the effect of acupuncture on stress reduction in women undergoing IVF and the majority have demonstrated a positive outcome. Moreover, a meta-analysis by Zheng et al. [25] demonstrated improvement in both clinical pregnancy rate and live birth rate in women undergoing IVF. Mind-body interventions have been shown to be an effective stress-management approach for numerous psychological conditions. A study by Domar et al. [26] found that mind-body interventions were associated with increased pregnancy rates when compared to control groups. A study by Oron et al. [27] showed that yoga improved anxiety, depression, and fertility-specific quality of life in infertility patients.

Pharmacologic interventions

Pharmacotherapy may be required for women with moderate to severe depression or anxiety or for women who experienced unsuccessful non-pharmacologic treatment. Pregnancy or desired pregnancy should not preclude a woman from receiving the care and pharmacologic intervention she requires. SSRIs are considered first-line pharmacotherapy for moderate to severe depression and anxiety.

SSRIs as a class have not been shown to significantly increase the incidence of neurologic/behavioral sequelae when used during pregnancy, persistent pulmonary hypertension of the neonate (PPHN), neonatal adaptation syndrome, or congenital malformations. However, conflicting data has limited the ability to create clear guidelines regarding SSRI use. Long-term studies have shown the neurodevelopment of an infant exposed to a SSRI in utero is not statistically different from the general population [28, 29]. Regarding PPHN, the incidence in the general population is 1 to 2 per 1000 and approximately 6 to 12 per 1000 in infants exposed to SSRIs. Recent studies show unlikely causative association between SSRI use and PPHN [30–32]. Neonatal adaptation syndrome is characterized as jitteriness, poor tone, hypoglycemia, hypothermia, weak or absent cry, and respiratory distress with potential desaturation during feeding. While neonatal adaptation syndrome affects approximately 30% of infants exposed to antidepressant medication in the 3rd trimester, it is fortunately a self-limiting disorder that typically resolves within the first 5 days of life without long-term sequelae [33].

The overall risk of congenital malformation in the general population ranges from 2 to 5%, similar to the risk of women taking SSRI medication. After adjusting for confounding factors, most studies have synthesized a lack of causative association or statistical significance between SSRI use and major congenital anomalies [34, 35]. Of note, of all the SSRIs, paroxetine has been identified as potentially teratogenic and implicated in several studies to be associated with congenital heart defects, specifically atrial and ventricular septal defects [35, 36]. While these claims have since been refuted in recent studies [37–39], paroxetine's FDA class has changed from C to D and it is no longer considered a first-line SSRI during pregnancy. The American College of Obstetricians and Gynecologists recommends fetal cardiac evaluation via directed fetal echocardiogram during the antepartum period [40]. However, if this is the only medication that has worked appropriately for the patient, one should consider continuing the paroxetine in pregnancy, after discussing the risks and benefits of medication continuation versus untreated depression.

Implications of psychiatric medications taken at the time of infertility treatments are less studied, although there is reassuring safety data. Akioyamen et al. [41] conducted a systematic review and reported that several studies concluded that there was no impact on gamete quality or pregnancy success in patients who were using antidepressants.

At times, women may not respond to SSRIs or may already be prescribed a different antidepressant and need medication recommendations. Generally, if a woman has a side effect with an SSRI, it is reasonable to switch to another SSRI. If the patient is on a therapeutic dose of an SSRI for at least 6 weeks and has not noted a benefit, it is reasonable to consider an antidepressant from a different class. Serotonin-norepinephrine reuptake inhibitors (SNRIs) have been studied in pregnancy and also show reassuring data related to safety in pregnancy, as do the atypical antidepressants. If a woman has a significant psychiatric history and is stable on an SNRI or an

atypical antidepressant, she should continue on that medication instead of attempting to convert to an SSRI. Women desiring pregnancy should be placed on the lowest effective dose required to elicit remission of symptoms (Table 1).

Due to the stress related to infertility and artificial reproductive technology, reproductive endocrinology and infertility (REI) physicians may be more likely to encounter patients with depression and/or anxiety. Many clinics, including our own, have a psychologist as an active part of the program for counseling pre- and post-treatment. Patient Health Questionnaire-9 is a helpful tool to utilize in identifying these patients and guiding the initiation of appropriate therapy. While some REI physicians are comfortable starting patients on psychiatric medications, others may refer patients to PCPs or psychiatrists for this role. Reasonable starting doses are described in Table 1. Understanding that it may take 4 to 6 weeks for medications to become effective, further management should be recommended on an individual basis with medication titration or referral as necessary. Certainly, cognitive-behavioral therapy should be encouraged and discussed with the patient, as the pharmacologic and non-pharmacologic interventions together have a synergistic effect.

Discussion

Based on the information reviewed in this commentary we would suggest the following for our cases.

Scenario 1

Patient 1 is currently stable and doing well psychiatrically while being prescribed bupropion. If she had a single episode of depression in the past that was considered mild to moderate, it would certainly be reasonable to discuss tapering off the medication prior to conception. Additionally, she could be offered psychotherapy initiation. This would allow her to proceed with IVF without concern for exposure to psychiatric medications, which is reasonable if she is in remission with her depressive symptoms.

If she had long-standing depression in the past where she attempted to discontinue bupropion and had worsening depression, we would recommend that she consider remaining on an antidepressant during infertility treatment. We would also recommend that she consider adding psychotherapy for further psychiatric benefit. With regard to medication options if she is naïve to other antidepressants, we would recommend discussing a switch from bupropion to an SSRI. We prefer sertraline as a first-line antidepressant whenever possible due to the abundance of data available for this drug. If she has been on several different antidepressants and bupropion offered the most benefit, we would continue that medication. We would have a discussion about switching to an SSRI as there is significantly more patient safety literature available regarding SSRIs when compared to bupropion.

Scenario 2

Patient 2 has symptoms that are consistent with a new diagnosis of depression. She has no history of prior depression and has not attempted any available options. It would be appropriate to discuss treatment options with Patient 2 that include therapy, medications, complementary options, or a combination of the above. If her symptoms are mild, she may elect to have therapy or acupuncture. If the therapies are not helpful, or if she is unable/unwilling to begin with those options, she could also be offered an antidepressant for treatment. We would recommend starting with an SSRI and maintaining her on the lowest, most effective dose required to remit her symptoms. It is important to educate patients that antidepressants typically take 4 to 6 weeks to affect notable improvements in mood at therapeutic levels. If she is started on an SSRI and is unable to tolerate it due to side effects, it is reasonable to change to another SSRI that may not share that side

Table 1 Summary of drug data

Recommendations*	Drug	Starting dose per day (mg)	Total dose per day (mg)
	Selective serotonin reuptake inhibitors (SSRI)		
1	Sertraline	50	50 to 150
2	Fluoxetine	10	10 to 60
3	Citalopram	20	20 to 40
4	Escitalopram	10	10 to 20
	Serotonin-norepinephrine reuptake inhibitors (SNRI)		
5	Venlafaxine	37.5 to 75	75 to 225
6	Duloxetine	20 to 30	20 to 60
	Atypical antidepressants		
7	Mirtazapine	15	15 to 30
8	Bupropion	75	150 to 300

* The authors have ordered these drugs from the most recommended (1) to the least recommended (8)

effect. For example, if the patient is started on sertraline and complains of significant sedation, she could switch to fluoxetine, which is more "activating" and would be less likely to cause sedation.

Conclusions

Understanding the symptoms and implications of mood disorders in infertility patients is imperative for the reproductive endocrinologist and infertility specialist. Identification of treatable mood symptoms during infertility treatments is beneficial for fertility, subsequent pregnancy, and a woman's mental well-being. Having a high index of suspicion and resources available for referral are imperative. Patient education and open discussions of stress and mood dysregulation that occurs with infertility will allow for an increased likelihood of identifying women suffering from depression, anxiety, and stress and an increased rate of intervention.

Acknowledgments The authors acknowledge Judy T. Walsh (Department of Obstetrics and Gynecology, University of Florida College of Medicine) for her editorial assistance.

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