# Psychiatric Aspects of Infertility

Madeleine A. Becker, M.D., Ann Chandy, M.D., Jessica L.W. Mayer, M.D., Jyoti Sachdeva, M.D., Elizabeth S. Albertini, M.D., Catherine Sham, B.A., Linda L.M. Worley, M.D.

Worldwide, 8–30% of reproductive aged couples suffer from infertility—which is defined as "an inability to conceive after 12 months of regular, unprotected sexual intercourse, or an impairment of a person's capacity to reproduce either as an individual or with his or her partner" (Vander Borght et al. 2018; Zegers-Hochschild et al. 2017; Shreffler et al. 2017; Winters and Walsh 2014). In the United States, the estimated prevalence of infertility is between 6% and 18%, and increases with advancing age (Chandra et al. 2013; Thoma et al. 2013).

The purpose of this resource document is to raise awareness about infertility and its profound impact and to provide an update for our field from the current literature to guide optimal care.

## PSYCHOLOGICAL IMPACT OF INFERTILITY

The psychological impact of being unable to conceive despite trying is that of a profound loss and a significant life crisis (Kohan et al. 2015). Many individuals suffer in isolation, unaware that infertility is highly prevalent, afflicting approximately one in eight couples worldwide. The feelings and reactions to infertility are complex, ranging from anger with self for the failure of one's body to procreate (Kohan et al. 2015) to an associated decrease in sexual desire, an impaired orgasmic function, and a loss of sexual satisfaction when 'sex by the clock for procreation' is required (Kohan et al. 2015; Marci et al. 2012). Couples may feel socially excluded, negatively stigmatized (Ergin et al. 2018), and may find it particularly painful to be around other couples with children or with unaware extended family members who make insensitive comments. Women trying to conceive face profound sadness and grief with each returning menstrual cycle. Seeking treatment with an infertility healthcare provider requires significant sacrifice of time, privacy, and money with no guarantee of conception or a successful birth. This can be disempowering, stressful, frustrating, and, at times, profoundly sad.

Couples may be reluctant to disclose psychological distress to their healthcare providers for fear this acknowledgement could jeopardize their candidacy for participation or continuation in assisted reproductive technologies. Couples may also keep their struggles with infertility private, isolating themselves from family, friends, and colleagues who could offer support (Ergin et al. 2018).

In addition to the substantial financial costs associated with fertility treatments, access to care is geographically limited and few states (currently 13) mandate some form of insurance coverage for infertility treatments. Discriminatory practices can further limit access for LGBT minority populations (currently 2.8–5.6% of the U.S. population) who are increasingly seeking assisted reproductive technologies (Kessler et al. 2013; Wu et al. 2017).

## INFERTILITY AND PSYCHIATRIC COMORBIDITY

There is a known association between eating disorders and infertility, with anorexia and bulimia nervosa accounting for up to 60% of cases of anovulatory infertility (ESHRE Capri, et al. 2006). A link between infertility, anxiety, and depressive disorders has also been reported (Gameiro et al. 2015; Domar et al. 1992; Anderson et al. 2003; Volgsten et al. 2008; Sejbaek et al. 2013; Holley et al. 2015; Lakatos et al. 2017). It is unclear whether premorbid diagnoses of anxiety and/or depression contribute to infertility or whether they result from the psychological distress of infertility and its treatments. There is a high prevalence of these disorders among infertile women with up to 40% meeting criteria for a psychiatric diagnosis; with generalized anxiety disorders most prevalent, followed by major depressive disorder, and then dysthymia. An increased risk of suicidal ideation has been reported in women who suffer from infertility, (e.g. a 9.4% incidence) (Shani et al. 2016) with even higher risks for women who were not able to successfully have a child after assisted reproductive treatments (Kjaer et al. 2011). Despite these high rates of psychiatric comorbidity, very few patients seek psychiatric care- one study noting only 6.7% of patients sought care (Chen et al. 2004).

Regarding premorbid anxiety and depressive disorders, what is clear is that pretreatment levels of depression and anxiety and past episodes of major depression are significant predictors of depression during infertility treatment (Holley et al. 2015). While the annual prevalence rate for major depressive disorder is 8.4% in women and 5.2% in men in the United States, it has been documented to rise to 39.1% for infertile women and 15.3% for infertile men (Holley et al. 2015). Dozens of studies have investigated this relationship between psychiatric illness prior to or during as-

sisted reproductive treatments to subsequent pregnancy rates, with conflicting results. A large meta-analysis by Matthiesen et al. (2011) did not find a significant influence of depression diagnosed before assisted reproductive therapy on the number of achieved pregnancies. Another recent large meta-analysis found that women who achieved pregnancy had significantly lower depression and state anxiety scores during assisted reproductive treatment than women who did not become pregnant; however, changes in depression and anxiety scores from baseline (before treatment) were not associated with assisted reproductive treatment outcomes (Purewal et al. 2018).

Various factors have been investigated for their contribution to the development of new onset psychiatric disorders during the course of infertility treatments. Most demographic features e.g. age, education level, spouse's age and education level, income, years of marriage, years of infertility, and previous assisted reproductive treatments were not found to be risk factors for psychiatric comorbidities. Psychological triggers for the development of depression and anxiety during infertility treatment are often social concerns; wanting to conform to social expectations by becoming a parent, loss of sexual self-esteem and enjoyment; scheduling sexual activity, fear of advancing age, financial concerns due to expense of treatments, and impairment in quality of life (Lakatos et al. 2017; Gdańska et al. 2017). Often these stressors peak around 4-6 years after diagnosis of infertility and after infertility treatment failures (Ramezanzadeh et al. 2004; Maroufizadeh et al. 2015). In addition, medications often used to treat infertility also can contribute to symptoms of anxiety, depression, and irritability (Rooney & Domar 2018). While partner support may be a protective factor against the development of depression, few studies have looked at gender differences in relation to the development of psychopathology. While both men and women experience distress during in-vitro fertilization (IVF), women report higher psychological distress than men across several domains including anxiety, depression, and low self-esteem (Ying et al. 2016; El Kissi et al. 2013). Overall, women report higher levels of anxiety symptoms when compared to men, though both suffer from higher levels of anxiety and depression during treatment compared to the general population (Holley et al. 2015).

The relationship between psychiatric illness and infertility is complex. Some illnesses pre-date infertility treatments and others are a result of infertility and its treatments. Untreated anxiety and depressive disorders may contribute to barriers in seeking assisted reproductive technologies (Herbert et al. 2010; Crawford et al. 2017) and to the discontinuation of treatment prematurely when chances for achieving a pregnancy are still good (Domar et al. 2010).

## PSYCHIATRIC SIDE EFFECTS OF HORMONAL TREATMENTS FOR INFERTILITY

Some women experience mood fluctuations related to normal hormonal changes during their natural reproductive cycles (Schmidt et al. 1998). Fertility medications target these same hormones in the hypothalamic pituitary ovarian axis and can have similar effects on mood (Garcia-Velasco & Fatemi 2015; Merari et al. 1992). Commonly used medications in fertility treatment alter levels of thyroid hormone, prolactin, estradiol, progestogens, GnRH, and gonadotrophs.

Hypothyroidism and hyperprolactinemia are treatable causes of infertility. Thyroid replacement hormone reduces depressive symptoms (Redmond 2004). Dopamine agonists, e.g. bromocriptine and cabergoline, treat infertility secondary to hyperprolactinemic anovulation (Usadi & Merriam 2015) and may increase the risk of impulse control disorders (Thondam et al. 2013; Falhammar & Yarker 2009) and psychotic symptoms (Shibli-Rahhal and Schlechte 2008; Seeman 2015; Snellen et al. 2016). They can also trigger dopamine toxicity when combined with antidepressants such as bupropion or venlafaxine (Burns 2007).

Combination oral contraceptive pills (OCPs) are often utilized to synchronize an IVF cycle to a particular schedule (Garcia-Velasco & Fatemi 2015). There is strong association between mood and fluctuations in estrogen and progesterone levels (Schmidt et al. 1998; Bloch et al. 2011) with estradiol and progestogens contributing to symptoms of depression, anxiety, and decreased libido (Lolak et al. 2005; Stenbæk et al. 2015; Fortin et al. 1972). These symptoms are often more clinically impairing in women with a history of depressive disorders and increase their risk for recurrent episodes of psychiatric illness (Fortin et al. 1972; Harlow et al. 1999; Harlow et al. 2003; Lolak et al. 2005; Singata-Madliki et al. 2016).

Selective estrogen receptor modulators (SERMs)—such as clomiphene citrate and tamoxifen—and aromatase inhibitors—such as letrozole—are commonly used for ovarian stimulation and for off-label use in men to increase spermatogenesis (Steiner et al. 2005; Rambhatla et al. 2016; Aussedat et al. 2017). Adverse psychological events related to these medications are well documented in women and in rare case reports in men (Aussedat et al. 2017) including reports of transient psychotic episodes related clomiphene (Siedentopf et al. 1997; Seeman 2015a). Because of their reduction in estrogen, the most commonly experienced side effects of these medications resemble those in menopause— including insomnia, decreased libido, and mood swings (Harlow et al. 1999).

Injectable medications (e.g. GnRH agonists, GnRH antagonists, and gonadotropins like FSH) induce production of multiple follicles in IVF cycles (Bloch et al. 2011). These medications have been found to correlate with symptoms of anxiety and depression through pituitary down-regulation resulting in hypogonadism (de Klerk et al. 2006; Schmidt et al. 1998; Bloch et al. 2011; Stenbæk et al. 2015). Hypogonadotropic states are associated with anhedonia, fatigue, anxiety, insomnia, decreased libido, and depressed mood (Bloch et al. 2011; Stenbæk et al. 2015; Toren et al. 1996). The severity of these symptoms correlates with longer durations of treatment, previous failed assisted reproductive treatment cycles, and a prior history of psychiatric illness (Awwad et al. 2012; Mamata et al. 2015; Ogawa et al. 2011; Vahratian et al. 2011).

A second group of injectable medications (e.g. human chorionic gonadotropin (hCG) and human menopausal gonadotropins (hMG)) trigger ovulation and are structurally similar to FSH and LH and may trigger symptoms of anxiety (Bhongade et al. 2015b). This anxiety may also be amplified in anticipation of the invasive procedure that will follow in the next several hours or days to retrieve the oocytes (de Klerk et al. 2007; Awwad et al. 2012).

Overall, most medications used in treating infertility have some effect on mood. These symptoms are exacerbated by the realization of high rates of failure in fertility treatments, the invasive nature of medication administration, examinations, tests, and the prolonged pursuit of parenthood often for years without success (de Klerk et al. 2007). More research is indicated to further elucidate the connection between infertility interventions and psychiatric implications.

## PSYCHOTROPIC MEDICATIONS AND INFERTILITY

Theoretically, psychotropic medications may influence the reproductive function in both men and women. This may occur by affecting the levels of neurotransmitters, such as dopamine, serotonin and GABA, that are involved in the physiologic regulation of the male and female reproductive axes (Hendrick et al. 2000). Psychotropic medications may also alter the metabolism and protein binding of hormones, influencing the levels of sex steroids (Hendrick et al. 2000). However, a 2015 systematic review concluded that clinical studies have not demonstrated a deleterious effect of psychotropic medication on oocytes in terms of retrieval and pregnancy rates (Worly & Gur 2015). A majority of studies however, show an association between maternal psychiatric illness and decreased reproductive success, including lower rates of oocyte retrieval, lower rates of ongoing pregnancy, and dysregulation of the stress system (Worly & Gur 2015).

### Antidepressants

Fluctuations in female sex-hormone levels likely alter transmission of serotonin thereby influencing psychopathology (Hall & Steiner 2013; Frokjaer et al. 2015). Selective serotonin reuptake inhibitors (SSRIs) may increase FSH levels in women with decreased ovarian function, theoretically further decreasing their fertility (Shahine & Lathi 2006). One prospective cohort study among 957 women found that antidepressant use within a given menstrual cycle was associated with a lower probability of conceiving. However, the authors note that 'this study is unable to truly differentiate the effect of the underlying depression from the antidepressant (Casilla-Lennon et al. 2016). Most studies looking at the exposure to SSRIs during IVF show no difference in pregnancy outcomes when compared to control group (Serafini et al. 2009; Friedman et al. 2009). In addition, a recent retrospective cohort analysis showed that patients exposed to SSRIs in vivo did not demonstrate an increased rate of embryo aneuploidy in IVF, and concluded that the IVF outcomes of patients exposed to SSRIs do not differ from those of unexposed patients (Hernandez-Nieto et al. 2017)

In 2016, a nationwide register-based cohort study (n = 23,557) of nulliparous women in Sweden found slightly reduced odds of pregnancy and live birth among the 4.4% of women diagnosed with depression/anxiety and/or dispensed antidepressants before their first IVF cycle (adjusted odds ratio of 0.86 and 0.83, respectively), compared to controls. However, women with depression/anxiety without antidepressants had a more pronounced reduction in pregnancy and live birth (adjusted odds ratio of 0.58 and 0.60, respectively), implying that the underlying co-morbid psychiatric disorder may be important for the observed association. (Cesta et al. 2016).

In 2005, the US Food and Drug Administration (FDA) warned that early prenatal exposure to paroxetine may increase the risk of congenital cardiac malformations, and changed its pregnancy category from C to D. Following this, the American College of Obstetrics recommended that paroxetine should be avoided, if possible, in women planning pregnancy (ACOG Committee on Practice Bulletins-Obstetrics 2008). It should be noted that additional recent studies (Huybrechts et al. 2014) showed no substantial increased risk of cardiac malformations attributable to paroxetine.

Mirtazapine has been shown in animal studies to reverse cisplatin-induced infertility (Altuner et al. 2013), as well as cyclophosphamide-induced infertility (in combination with hesperidin) (Khedr 2015). It may attenuate the hypothalamic-pituitary-adrenocortical (HPA) hyperactivity in depressed patients (Schüle et al. 2003), which theoretically could improve reproductive outcomes given the suppressing effect of a chronically activated HPA axis on both female and male reproductive systems (Kalantaridou et al. 2010). However, no studies have looked at this association.

Most antidepressants (especially the SSRIs and venlafaxine), can negatively impact both female and male fertility by causing sexual dysfunction (Olivier et al. 2017; Clayton & Valladares Juarez 2017). However, as depressive disorder itself can cause decreased libido, the benefits of treating depressive disorder-induced sexual dysfunction versus the risks of antidepressant-induced sexual dysfunction must be weighed on a case-by-case basis. Alternatively, antidepressants that are not associated with decreased libido, including bupropion, mirtazapine, vortioxetine and vilazodone, may be considered (Olivier et al. 2017; Clayton & Valladares Juarez 2017).

### Mood Stabilizers and Antipsychotics

The risk of infertility can be increased by treatment with certain mood stabilizers. Studies show a significantly higher rate of menstrual cycle disorders, hyperandrogenism, and PCOS (which have been associated with infertility), in women receiving prolonged valproate therapy for bipolar disorder (Okanović & Zivanović 2016; Gotlib et al. 2017; Morrell et al. 2003). Given the risk of teratogenic effects (e.g., neural

tube defects), valproic acid should be avoided in women planning a pregnancy (Gotlib et al. 2017).

Additionally, given that obesity may predispose to, or be one of the risk factors for PCOS and subsequent infertility, the risk of psychotropic induced weight gain should be seriously considered in women planning pregnancy. Among the mood stabilizers, valproic acid, lithium, clozapine, olanzapine, quetiapine, and risperidone have the highest risk of problematic weight gain (Hasnain & Vieweg 2013).

While carbamazepine and oxcarbazepine do not appear to cause significant weight gain (Hasnain & Vieweg 2013), they may induce the metabolism of steroid hormones (Reimers 2016), and thus affect the efficacy of exogenous hormones administered during treatment for infertility. Furthermore, carbamazepine has been shown to increase serum sex hormone binding globulin (SHBG) concentrations. Over time the increase in serum SHBG levels leads to diminished bioactivity of estradiol, which may result in menstrual disorders in some women, and, thus, to reduced fertility (Isojärvi 2008). Lamotrigine levels may be decreased by oral contraceptives (Reimers 2016; Joffe 2007) administered during the initial phase of IVF treatment, and as such should be monitored during this period.

Women appear to be more sensitive to antipsychotic induced hyperprolactinemia, than men (Smith et al. 2002). Hyperprolactinemia can cause infertility via hypogonadism, menstrual disturbances and decreased libido (Bargiota et al. 2015; Smith 2003), and is seen in 48% of those on first generation antipsychotics, and 88% of those on risperidone (Kinon et al. 2003). Other second-generation antipsychotics, with a low affinity for dopamine-2 receptors, are mostly prolactin sparing.

### Benzodiazepines

Short acting benzodiazepines such as midazolam are often utilized in conscious sedation protocols during oocyte retrieval (Singhal et al. 2017) and have not been associated with negative reproductive outcomes (Bourgon et al. 2016; Kwan et al. 2018; Kwan et al. 2006). Contrast this with long-term benzodiazepine use, which has been found to significantly affect the secretion of pituitary hormones, (e.g. gonadotropins and prolactin) (Arvat et al. 2002) and has been associated with a decrease in fertility (Nillni et al. 2016).

### Cannabis

Cannabis, medicinal or otherwise, can cause menstrual and ovulation changes, decrease the oocyte retrieval rate during in vitro fertilization, and in animal models has induced embryo implantation failure (Wang et al. 2006).

### Other Psychotropics

There is, unfortunately, little published literature on the reproductive effects of methylphenidate and amphetamines, and most of it consists of animal studies. Indeed, a National Toxicology Program - Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR) Expert Panel Report on the reproductive and developmental toxicity of methylphenidate was impressed with "the paucity of interpretable toxicity data relevant to human therapeutic use" (Golub et al. 2005). Similarly, minimal data exist on the reproductive function effects of other psychotropics, e.g. buspirone, gabapentin, and pregabalin, and stimulants.

## NON-PHARMACOLOGICAL INTERVENTIONS IN INFERTILITY

There are limited data exploring non-pharmacologic interventions in the management of anxiety and depression related to infertility. Relevant articles include those that look at psychosocial interventions such as education, counseling, and specific types of therapy. Other articles explore the role of acupuncture and complementary medicine.

There are no clear guidelines on the management of comorbid psychiatric conditions during infertility treatment (Hoff et al. 2018). Psychosocial interventions, such as psychotherapy or infertility counseling, may be helpful in reducing infertility related distress in individuals and couples throughout assisted reproductive treatments. These interventions support individuals and couples during the failures of fertility intervention and can also be of great utility during treatment; with studies demonstrating improved individual psychological outcomes, marital relationships, pregnancy rates, and sexual functioning. There is little evidence, however, that these interventions reduce rates of psychiatric illnesses (Chow et al. 2016; Maleki-Saghooni et al. 2017; Winkelman et al. 2016; Schmidt et al. 2005; Kim et al. 2018; Gameiro et al. 2015; Galhardo et al. 2016). When such interventions are available, only 10-34% of patients utilize them, highlighting an area for improvement (Read et al. 2014).

Stress may be a contributing factor in infertility. One study measured levels of salivary-alpha-amylase, a biomarker of stress and showed that women with higher levels were twice as likely to experience infertility (Lynch et al. 2014). It may directly decrease libido or coital frequency or may cause increased cortisol production via the HPA axis. Increased cortisol may lead to inhibition of the GnRH or LH surge leading to anovulation (Campagne 2006). In males, psychological stress lowers total testosterone level with secondary rise in serum LH and FSH levels altering seminal quality (Bhongade et al. 2015a). Studies have shown higher pregnancy rates when infertile women are offered cognitive behavior therapy groups or mind-body intervention programs for stress reduction (Lynch et al. 2012).

In an analysis by Boivin et al, the authors evaluated 1,957 articles and books published on the psychological aspects of infertility in an effort to determine if psychosocial interventions improve well-being and pregnancy rates. They found that psychosocial interventions reduce negative affect but are less likely to impact function. Rates of pregnancy were not consistently impacted by these interventions, as only three studies showed a positive intervention effect and five studies showed no intervention effect. Education and skills training

classes were shown to have a more positive impact on mood than counseling sessions. Specific interventions included coping training, sex therapy, preparatory information, and relaxation training. Both men and women were found to benefit equally from psychosocial interventions (Boivin 2003).

Faramarzi et al., compared cognitive behavioral therapy (CBT) to fluoxetine pharmacotherapy in reducing anxiety and depressive symptoms related to infertility. CBT was composed of 10 sessions on relaxation, restructuring thoughts, and eliminating negative automatic thinking about fertility. Both Fluoxetine and CBT reduced levels of anxiety and depression, and improved social functioning, but CBT was more effective in reducing psychosomatic symptoms, (as measured by the psychosomatic subscale of the General Health Questionnaire (GHQ)) and in decreasing scores on the Beck Depression Inventory. Both groups had significantly better results than placebo (Faramarzi et al. 2008).

Complementary and Alternative Medicine (CAM) has been explored as a non-pharmacological intervention to treat mood symptoms during infertility but limited scientific evidence is available to date to support the its use. The impact of acupuncture on stress for women undergoing in vitro fertilization has been studied with favorable outcomes (Domar et al. 2009). In Balk et al (2010), women receiving acupuncture on the day of embryo transfer had lower perceived stress and higher rates of pregnancy than those who received placebo at a rate of 64.7% vs 42.5% without acupuncture. Additional studies examining diet and exercise have also been done. In one study, improvements in diet and exercise led to weight loss of 5-10% in obese women with PCOS and decreased levels of anxiety and depression (Clark et al. 2013). Overall, it does appear that weight loss and healthy lifestyle modifications positively benefit mood symptoms during fertility treatment. Given the desire of many women to have alternative options for the treatment of mood symptoms during infertility treatment, more studies are needed to better understand the impact of complementary medicine in this patient population.

## CONCLUSIONS

Infertility poses a significant psychological burden, and patients receiving assisted reproductive therapies are at risk for psychiatric comorbidity (Chen et al. 2004). Awareness of the potential psychological effects of infertility treatments is critical because many women are reluctant to discuss their distress and very few seek help. Deciphering grief reactions, bereavement, eating disorders, depressive or anxiety disorders, and medication side effects is important in determining optimal treatment for patients.

Depressive and anxiety disorders commonly affect women who are trying to conceive, although there are conflicting results regarding their effects on ability to conceive. It does appear that stress, anxiety, and depression may have both direct and indirect effects on fertility. Fertility medications also can impact mood. There are some risks to utilizing psychotropic medications during the time when trying to conceive; this varies according to the class and type of medication. Any risk must be considered in the context of indication for the patient and weighed against the impact of an untreated psychiatric illness. Psychotherapy can also play a role in the treatment of mood disorders. In some cases, alternative treatments can also help with managing mood symptoms both during and after infertility treatments.

### ARTICLE INFORMATION

Approved by the Joint Reference Committee, February 2019



### REFERENCES (UPDATED VIA PAPERPILE)

Abu-Tair, F., Strowitzki, T. & Bergemann, N., 2007. Exazerbation einer schizoaffektiven Psychose nach In-vitro-Fertilisation mit Leuprorelinacetat. Der Nervenarzt, 78(6), pp.691–695.

ACOG Committee on Practice Bulletins—Obstetrics, 2008. ACOG Practice Bulletin: Clinical management guidelines for obstetrician-gynecologists number 92, April 2008 (replaces practice bulletin number 87, November 2007). Use of psychiatric medications during pregnancy and lactation. Obstetrics and gynecology, 111(4), pp.1001–1020.

Altuner, D. et al., 2013. The effect of mirtazapine on cisplatin-induced oxidative damage and infertility in rat ovaries. TheScientificWorldJournal, 2013, p.327240.

Anderson, K.M. et al., 2003. Distress and concerns in couples referred to a specialist infertility clinic. Journal of psychosomatic research, 54(4), pp.353–355.

Arvat, E. et al., 2002. Benzodiazepines and anterior pituitary function. Journal of endocrinological investigation, 25(8), pp.735–747.

Aussedat, M. et al., 2017. Clomiphene for the Treatment of Male Infertility: A Case Report of Mood Change and a Literature Overview. Current drug safety, 12(3), pp.208–215.

Awwad, J.T. et al., 2012. An investigational ovarian stimulation protocol increased significantly the psychological burden in women with premature ovarian failure. Acta obstetricia et gynecologica Scandinavica, 91(11), pp.1273–1278.

Balk, J. et al., 2010. The relationship between perceived stress, acupuncture, and pregnancy rates among IVF patients: a pilot study. Complementary therapies in clinical practice, 16(3), pp.154–157.

Bargiota, S.I. et al., 2015. Hyperprolactinaemia: psychological aspects and menstrual attitudes of women with schizophrenia. Psychiatry research, 226(2-3), p.525.

Bhongade, M.B. et al., 2015a. Effect of psychological stress on fertility hormones and seminal quality in male partners of infertile couples. Andrologia, 47(3), pp.336–342.

Bhongade, M.B. et al., 2015b. Effect of psychological stress on fertility hormones and seminal quality in male partners of infertile couples. Andrologia, 47(3), pp.336–342.

Bloch, M. et al., 2011. GnRH-agonist induced depressive and anxiety symptoms during in vitro fertilization–embryo transfer cycles. Fertility and sterility, 95(1), pp.307–309.

Boivin, J., 2003. A review of psychosocial interventions in infertility. Social science & medicine, 57(12), pp.2325–2341.

Bourgon, N. et al., 2016. Impact of conscious sedation during oocyte retrieval on clinical pregnancy rate in assisted reproductive technology? An equivalence cohort study. European journal of obstetrics, gynecology, and reproductive biology, 206, pp.e19–e20.

Burns, L.H., 2007. Psychiatric aspects of infertility and infertility treatments. The Psychiatric clinics of North America, 30(4), pp.689–716.

Campagne, D.M., 2006. Should fertilization treatment start with reducing stress? Human reproduction , 21(7), pp.1651–1658.
Casilla-Lennon, M.M., Meltzer-Brody, S. & Steiner, A.Z., 2016. The effect of antidepressants on fertility. American journal of obstetrics and gynecology, 215(3), pp.314.e1–5.
Cesta, C.E. et al., 2016. Depression, anxiety, and antidepressant treatment in women: association with in vitro fertilization outcome. Fertility and sterility, 105(6), pp.1594–1602.e3.
Chandra, A. et al., 2013. Infertility and impaired fecundity in the United States, 1982-2010 data from the National Survey of Family Growth. National Health Statistics Report, 67, pp. 1-18.
Chen, T.-H. et al., 2004. Prevalence of depressive and anxiety disorders in an assisted reproductive technique clinic. Human reproduction , 19(10), pp.2313–2318.
Choi, S.-H. et al., 2005. Psychological side-effects of clomiphene citrate and human menopausal gonadotrophin. Journal of psychosomatic obstetrics and gynaecology, 26(2), pp.93–100.
Chow, K.-M., Cheung, M.-C. & Cheung, I.K., 2016. Psychosocial interventions for infertile couples: a critical review. Journal of clinical nursing, 25(15-16), pp.2101–2113.
Clark, N.A. et al., 2013. A systematic review of the evidence for complementary and alternative medicine in infertility. International Journal of Gynecology & Obstetrics, 122(3), pp.202–206.
Clayton, A.H. & Valladares Juarez, E.M., 2017. Female Sexual Dysfunction. Psychiatric Clinics, 40(2), pp.267–284.
Crawford, N.M., Hoff, H.S. & Mersereau, J.E., 2017. Infertile women who screen positive for depression are less likely to initiate fertility treatments. Human reproduction , 32(3), pp.582–587.
Domar, A.D. et al., 2010. A prospective investigation into the reasons why insured United States patients drop out of in vitro fertilization treatment. Fertility and sterility, 94(4), pp.1457–1459.
Domar, A.D. et al., 2009. The impact of acupuncture on in vitro fertilization outcome. Fertility and sterility, 91(3), pp.723–726.
Domar, A.D. et al., 1992. The prevalence and predictability of depression in infertile women. Fertility and sterility, 58(6), pp.1158–1163.
El Kissi, Y. et al., 2013. General psychopathology, anxiety, depression and self-esteem in couples undergoing infertility treatment: a comparative study between men and women. European journal of obstetrics, gynecology, and reproductive biology, 167(2), pp.185–189.
Ergin, R.N. et al., 2018. Social stigma and familial attitudes related to infertility. Turkish journal of obstetrics and gynecology, 15(1), pp.46–49.
ESHRE Capri Workshop, Group, 2006. Nutrition and reproduction in women. Human reproduction update, 12(3), pp.193-207.
Falhammar, H. & Yarker, J.Y., 2009. Pathological gambling and hypersexuality in cabergoline-treated prolactinoma. The Medical journal of Australia, 190(2), p.97.
Faramarzi, M. et al., 2008. Is psychotherapy a reliable alternative to pharmacotherapy to promote the mental health of infertile women? A randomized clinical trial. European journal of obstetrics, gynecology, and reproductive biology, 141(1), pp.49–53.
Fortin, J.N. et al., 1972. Side Effects of Oral Contraceptive Medication: A Psychosomatic Problem. Canadian Psychiatric Association journal, 17(1), pp.3–10.
Friedman, B.E. et al., 2009. Effect of selective serotonin reuptake inhibitors on in vitro fertilization outcome. Fertility and sterility, 92(4), pp.1312–1314.
Frokjaer, V.G. et al., 2015. Role of Serotonin Transporter Changes in Depressive Responses to Sex-Steroid Hormone Manipulation: A Positron Emission Tomography Study. Biological psychiatry, 78(8), pp.534–543.
Galhardo, A. et al., 2016. The infertility trap: how defeat and entrapment affect depressive symptoms. Human reproduction , 31(2), pp.419–426.
Gameiro, S. et al., 2015. ESHRE guideline: routine psychosocial care in infertility and medically assisted reproduction—a guide for fertility staff. Human reproduction , 30(11), pp.2476–2485.
Garcia-Velasco, J.A. & Fatemi, H.M., 2015. To pill or not to pill in GnRH antagonist cycles: that is the question! Reproductive biomedicine online, 30(1), pp.39–42.
Gdańska, P. et al., 2017. Anxiety and depression in women undergoing infertility treatment. Ginekologia polska, 88(2), pp.109–112.
Golub, M. et al., 2005. NTP-CERHR Expert Panel Report on the reproductive and developmental toxicity of amphetamine and methamphetamine. Birth defects research. Part B, Developmental and reproductive toxicology, 74(6), pp.471–584.
Gotlib, D. et al., 2017. Valproic Acid in Women and Girls of Childbearing Age. Current psychiatry reports, 19(9), p.58.
Hall, E. & Steiner, M., 2013. Serotonin and female psychopathology. Women's health , 9(1), pp.85–97.
Harlow, B.L. et al., 2003. Depression and its influence on reproductive endocrine and menstrual cycle markers associated with perimenopause: the Harvard Study of Moods and Cycles. Archives of general psychiatry, 60(1), pp.29–36.
Harlow, B.L. et al., 1999. Prevalence and predictors of depressive symptoms in older premenopausal women: the Harvard Study of Moods and Cycles. Archives of general psychiatry, 56(5), pp.418–424.
Hasnain, M. & Vieweg, W.V.R., 2013. Weight considerations in psychotropic drug prescribing and switching. Postgraduate medicine, 125(5), pp.117–129.
Hendrick, V. et al., 2000. Antidepressant medications, mood and male fertility. Psychoneuroendocrinology, 25(1), pp.37–51.
Herbert, D.L., Lucke, J.C. & Dobson, A.J., 2010. Depression: an emotional obstacle to seeking medical advice for infertility. Fertility and sterility, 94(5), pp.1817–1821.
Hernandez-Nieto, C. et al., 2017. Embryo aneuploidy is not impacted by selective serotonin reuptake inhibitor exposure. Fertility and sterility, 108(6), pp.973–979.
Hoff, H.S., Crawford, N.M. & Mersereau, J.E., 2018. Screening for Psychological Conditions in Infertile Women: Provider Perspectives. Journal of women's health , 27(4), pp.503–509.
Holley, S.R. et al., 2015. Prevalence and predictors of major depressive disorder for fertility treatment patients and their partners. Fertility and sterility, 103(5), pp.1332–1339.
Huybrechts, K.F. et al., 2014. Antidepressant use in pregnancy and the risk of cardiac defects. The New England journal of medicine, 370(25), pp.2397–2407.
Isojärvi, J., 2008. Disorders of reproduction in patients with epilepsy: antiepileptic drug related mechanisms. Seizure: the journal of the British Epilepsy Association, 17(2), pp.111–119.
Joffe, H., 2007. Reproductive biology and psychotropic treatments in premenopausal women with bipolar disorder. The Journal of clinical psychiatry, 68 Suppl 9, pp.10–15.
Kalantaridou, S.N. et al., 2010. Corticotropin-releasing hormone, stress and human reproduction: an update. Journal of reproductive immunology, 85(1), pp.33–39.
Kessler, L.M. et al., 2013. Infertility evaluation and treatment among women in the United States. Fertility and sterility, 100(4), pp.1025–1032.
Khedr, N.F., 2015. Protective effect of mirtazapine and hesperidin on cyclophosphamide-induced oxidative damage and infertility in rat ovaries. Experimental biology and medicine, 240(12), pp.1682–1689.
Kim, J.H., Shin, H.S. & Yun, E.K., 2018. A Dyadic Approach to Infertility Stress, Marital Adjustment, and Depression on Quality of Life in Infertile Couples. Journal of holistic nursing: official journal of the American Holistic Nurses' Association, 36(1), pp.6–14.
Kinon, B.J. et al., 2003. Prevalence of hyperprolactinemia in schizophrenic patients treated with conventional antipsychotic medications or risperidone1. Psychoneuroendocrinology, 28, pp.55–68.
Kjaer, T.K. et al., 2011. Suicide in Danish women evaluated for fertility problems. Human reproduction , 26(9), pp.2401–2407.
de Klerk, C. et al., 2007. The psychological impact of IVF failure after two or more cycles of IVF with a mild versus standard treatment strategy. Human reproduction , 22(9), pp.2554–2558.

de Klerk, C. et al., 2006. The psychological impact of mild ovarian stimulation combined with single embryo transfer compared with conventional IVF. Human reproduction , 21(3), pp.721–727.

Kohan, S., Ghasemi, Z. & Beigi, M., 2015. Exploring infertile women's experiences about sexual life: A qualitative study. Iranian journal of nursing and midwifery research, 20(1), pp.34–39.

Kwan, I. et al., 2006. Conscious sedation and analgesia for oocyte retrieval during IVF procedures: a Cochrane review. Human reproduction , 21(7), pp.1672–1679.

Kwan, I. et al., 2018. Pain relief for women undergoing oocyte retrieval for assisted reproduction. Cochrane database of systematic reviews , 5, p.CD004829.

Lakatos, E. et al., 2017. Anxiety and depression among infertile women: a cross-sectional survey from Hungary. BMC women's health, 17(1), p.48.

Leyser-Whalen, O., 2014. "Crazy Woman Juice": Making Sense of Women's Clomiphene Infertility Treatments. Women's Reproductive Health, 1(2), pp.73–89.

Lolak, S., Rashid, N. & Wise, T.N., 2005. Interface of Women's Mental and Reproductive Health. Current psychiatry reports, 7(3), pp.220–227.

Lynch, C.D. et al., 2012. Are increased levels of self-reported psychosocial stress, anxiety, and depression associated with fecundity? Fertility and sterility, 98(2), pp.453–458.

Lynch, C.D. et al., 2014. Preconception stress increases the risk of infertility: results from a couple-based prospective cohort study—the LIFE study. Human reproduction , 29(5), pp.1067–1075.

Maleki-Saghooni, N. et al., 2017. Effectiveness of infertility counseling on pregnancy rate in infertile patients undergoing assisted reproductive technologies: A systematic review and meta-analysis. International journal of reproductive biomedicine (Yazd, Iran), 15(7), pp.391–402.

Mamata, D. et al., 2015. Impact of different controlled ovarian stimulation protocols on the physical and psychological burdens in women undergoing in vitro fertilization/intra cytoplasmic sperm injection. Journal of human reproductive sciences, 8(2), pp.86–92.

Marci, R. et al., 2012. Procreative sex in infertile couples: the decay of pleasure? Health and quality of life outcomes, 10, p.140.

Maroufizadeh, S. et al., 2015. Anxiety and depression after failure of assisted reproductive treatment among patients experiencing infertility. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics, 130(3), pp.253–256.

Matthiesen, S.M.S. et al., 2011. Stress, distress and outcome of assisted reproductive technology (ART): a meta-analysis. Human reproduction , 26(10), pp.2763–2776.

Merari, D. et al., 1992. Psychological and hormonal changes in the course of in vitro fertilization. Journal of assisted reproduction and genetics, 9(2), pp.161–169.

Morrell, M.J. et al., 2003. Higher androgens and weight gain with valproate compared with lamotrigine for epilepsy. Epilepsy research, 54(2-3), pp.189–199.

Nillni, Y.I. et al., 2016. Depression, anxiety, and psychotropic medication use and fecundability. American journal of obstetrics and gynecology, 215(4), pp.453.e1–8.

Ogawa, M., Takamatsu, K. & Horiguchi, F., 2011. Evaluation of factors associated with the anxiety and depression of female infertility patients. BioPsychoSocial medicine, 5(1), p.15.

Okanović, M. & Zivanović, O., 2016. VALPROATE, BIPOLAR DISORDER AND POLYCYSTIC OVARIAN SYNDROME. Medicinski pregled, 69(3-4), pp.121–126.

Olivier, J.D.A. et al., 2017. Sexual Dysfunction, Depression and Antidepressants: A Translational Approach. In B. Olivier, ed. Sexual Dysfunction. InTech.

Parikh, A.R. & Liskow, B.I., 2007. Manic delirium associated with clomiphene-induced ovulation. Psychosomatics, 48(1), pp.65–66.

Pasch, L.A. et al., 2016. Addressing the needs of fertility treatment patients and their partners: are they informed of and do they receive mental health services? Fertility and sterility, 106(1), pp.209–215.e2.

Purewal, S., Chapman, S.C.E. & van den Akker, O.B.A., 2018. Depression and state anxiety scores during assisted reproductive treatment are associated with outcome: a meta-analysis. Reproductive biomedicine online, 36(6), pp.646–657.

Rambhatla, A., Mills, J.N. & Rajfer, J., 2016. The Role of Estrogen Modulators in Male Hypogonadism and Infertility. Reviews in urology, 18(2), pp.66–72.

Ramezanzadeh, F. et al., 2004. A survey of relationship between anxiety, depression and duration of infertility. BMC women's health, 4(1), p.9.

Read, S.C. et al., 2014. Psychosocial services for couples in infertility treatment: what do couples really want? Patient education and counseling, 94(3), pp.390–395.

Redmond, G.P., 2004. Thyroid dysfunction and women's reproductive health. Thyroid: official journal of the American Thyroid Association, 14 Suppl 1, pp.S5–15.

Reimers, A., 2016. Contraception for women with epilepsy: counseling, choices, and concerns. Open access journal of contraception, 7, pp.69–76.

Rodrigues, J.D.M., Lapa, M.G.S. & Brockington, I.F., 2014. Psychotic episode secondary to gonadotrophins. General hospital psychiatry, 36(5), pp.549.e7–8.

Rooney, K.L. & Domar, A.D., 2018. The relationship between stress and infertility. Dialogues in clinical neuroscience, 20(1), pp.41–47.

Schmidt, L., Christensen, U. & Holstein, B.E., 2005. The social epidemiology of coping with infertility. Human reproduction , 20(4), pp.1044–1052.

Schmidt, P.J. et al., 1998. Differential behavioral effects of gonadal steroids in women with and in those without premenstrual syndrome. The New England journal of medicine, 338(4), pp.209–216.

Schüle, C. et al., 2003. Attenuation of hypothalamic-pituitary-adrenocortical hyperactivity in depressed patients by mirtazapine. Psychopharmacology, 166(3), pp.271–275.

Seeman, M.V., 2015a. Transient psychosis in women on clomiphene, bromocriptine, domperidone and related endocrine drugs. Gynecological endocrinology: the official journal of the International Society of Gynecological Endocrinology, 31(10), pp.751–754.

Seeman, M.V., 2015b. Transient psychosis in women on clomiphene, bromocriptine, domperidone and related endocrine drugs. Gynecological endocrinology: the official journal of the International Society of Gynecological Endocrinology, 31(10), pp.751–754.

Sejbaek, C.S. et al., 2013. Incidence of depression and influence of depression on the number of treatment cycles and births in a national cohort of 42,880 women treated with ART. Human reproduction , 28(4), pp.1100–1109.

Serafini, P. et al., 2009. Fluoxetine treatment for anxiety in women undergoing in vitro fertilization. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics, 105(2), pp.136–139.

Shahine, L.K. & Lathi, R.B., 2006. Night sweats and elevated follicle-stimulating hormone levels while taking selective serotonin reuptake inhibitors. Obstetrics and gynecology, 108(3 Pt 2), pp.741–742.

Shani, C. et al., 2016. Suicidal risk among infertile women undergoing in-vitro fertilization: Incidence and risk factors. Psychiatry research, 240, pp.53–59.

Shibli-Rahhal, A. & Schlechte, J.A., 2008. Prolactinomas: Diagnosis and~Management. In B. Swearingen & B. M. K. Biller, eds. Diagnosis and Management of Pituitary Disorders. Totowa, NJ: Humana Press, pp. 125–140.

Shreffler, K.M., Greil, A.L. & McQuillan, J., 2017. Responding to Infertility: Lessons From a Growing Body of Research and Suggested Guidelines for Practice. Family relations, 66(4), pp.644–658.

Siedentopf, F. et al., 1997. Clomiphene citrate as a possible cause of a psychotic reaction during infertility treatment. Human reproduction , 12(4), pp.706–707.

Singata-Madliki, M., Hofmeyr, G.J. & Lawrie, T.A., 2016. The effect of depot medroxyprogesterone acetate on postnatal depression: a randomised controlled trial. The journal of family planning and reproductive health care / Faculty of Family Planning & Reproductive Health Care, Royal College of Obstetricians & Gynaecologists, 42(3), pp.171–176.

Singhal, H. et al., 2017. Patient Experience with Conscious Sedation as a Method of Pain Relief for Transvaginal Oocyte Retrieval: A Cross Sectional Study. Journal of human reproductive sciences, 10(2), pp.119–123.

Skovlund, C.W. et al., 2016. Association of Hormonal Contraception With Depression. JAMA psychiatry , 73(11), pp.1154–1162.

Smith, S., 2003. Effects of antipsychotics on sexual and endocrine function in women: implications for clinical practice. Journal of clinical psychopharmacology, 23(3 Suppl 1), pp.S27–32.

Smith, S. et al., 2002. The effects of antipsychotic-induced hyperprolactinaemia on the hypothalamic-pituitary-gonadal axis. Journal of clinical psychopharmacology, 22(2), pp.109–114.

Snellen, M. et al., 2016. Pharmacological lactation suppression with D2 receptor agonists and risk of postpartum psychosis: A systematic review. The Australian & New Zealand journal of obstetrics & gynaecology, 56(4), pp.336–340.

Steiner, A.Z., Terplan, M. & Paulson, R.J., 2005. Comparison of tamoxifen and clomiphene citrate for ovulation induction: a meta-analysis. Human reproduction , 20(6), pp.1511–1515.

Stenbæk, D.S. et al., 2015. Mental distress and personality in women undergoing GnRH agonist versus GnRH antagonist protocols for assisted reproductive technology. Human reproduction , 30(1), pp.103–110.

Stenbæk, D.S. et al., 2016. Sex hormone manipulation slows reaction time and increases labile mood in healthy women. Psychoneuroendocrinology, 68, pp.39–46.

Thoma, ME. et al., 2013. Prevalence of infertility in the United States as estimated by the current duration approach and traditional constructed approach. Fertility and Sterility, 99(5), pp. 1324-1331.

Thondam, S.K. et al., 2013. Impulse control disorder in a patient on long-term treatment with bromocriptine for a macroprolactinoma. Clinical neuropharmacology, 36(5), pp.170–172.

Toftager, M. et al., 2018. Quality of life and psychosocial and physical well-being among 1,023 women during their first assisted reproductive technology treatment: secondary outcome to a randomized controlled trial comparing gonadotropin-releasing hormone (GnRH) antagonist and GnRH agonist protocols. Fertility and sterility, 109(1), pp.154–164.

Toren, P. et al., 1996. Depression in women treated with a gonadotropinreleasing hormone agonist. Biological psychiatry, 39(5), pp.378–382.

Usadi, R.S. & Merriam, K.S., 2015. On-label and off-label drug use in the treatment of female infertility. Fertility and sterility, 103(3), pp.583–594.

Vahratian, A. et al., 2011. Longitudinal depressive symptoms and state anxiety among women using assisted reproductive technology. Fertility and sterility, 95(3), pp.1192–1194.

Vander Borght, M., Borght, M.V. & Wyns, C., 2018. Fertility and infertility: Definition and epidemiology. Clinical biochemistry. Available at: http://dx.doi.org/10.1016/j.clinbiochem.2018.03.012.

Volgsten, H. et al., 2008. Prevalence of psychiatric disorders in infertile women and men undergoing in vitro fertilization treatment. Human reproduction , 23(9), pp.2056–2063.

Wang, H., Dey, S.K. & Maccarrone, M., 2006. Jekyll and hyde: two faces of cannabinoid signaling in male and female fertility. Endocrine reviews, 27(5), pp.427–448.

Winkelman, W.D. et al., 2016. The Sexual Impact of Infertility Among Women Seeking Fertility Care. Sexual medicine today, 4(3), pp.e190–7.

Winters, B.R. & Walsh, T.J., 2014. The epidemiology of male infertility. The Urologic clinics of North America, 41(1), pp.195–204.

Worly, B.L. & Gur, T.L., 2015. The effect of mental illness and psychotropic medication on gametes and fertility: a systematic review. The Journal of clinical psychiatry, 76(7), pp.974–985.

Wu, H.Y. et al., 2017. Lesbian, gay, bisexual, transgender content on reproductive endocrinology and infertility clinic websites. Fertility and sterility, 108(1), pp.183–191.

Ying, L., Wu, L.H. & Loke, A.Y., 2016. Gender differences in emotional reactions to in vitro fertilization treatment: a systematic review. Journal of assisted reproduction and genetics, 33(2), pp.167–179.

Zegers-Hochschild, F. et al., 2017. The International Glossary on Infertility and Fertility Care, 2017. Human reproduction , 32(9), pp.1786–1801.