Mental Disorders and Female Infertility.

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Introduction

Raising children is a cherished process associated with high expectations of rewards. Parenthood yields substantial and enduring improvements to quality of life; however, the stress and expense involved in raising children partially offsets these benefits (Pollmann-Schult, 2014). Infertility is frequently distressing and often triggers negative emotions, including shame, guilt, anxiety and sadness.

Reproduction is not the primary goal of self-regulation in the human body; rather, it is the maintenance of the brain’s energy...
supply (Peters et al., 2004). Reproduction is a secondary goal and not pursued when there is a food shortage, when facing perilous threats or when lacking social support. Random reproduction may endanger “inclusive fitness” reducing the probability of the organism and related organisms to propagate their genes. (Vitzthum, 2008) It is therefore logical that metabolic and behavioral regulatory systems within the brain are connected with the central regulation of fertility. What follows is a reproductive system with high sensitivity to changes within its nutritional or social environment. For these reasons, it is helpful to apply the combined knowledge from gynecological endocrinology and reproductive medicine with knowledge from the behavioral sciences and neurobiology when counseling women with infertility.

A review of the literature was performed using the PubMed database. A search was conducted using the keywords “infertility” and “mental disorders” and included only studies between 2012 and 2018. The results included 251 abstracts that were manually searched. Additionally, prior review articles (Williams et al., 2007a; Schweiger and Strowitzki, 2012; Hanson et al., 2017) were tracked.

**Epidemiology and mechanisms of infertility**

Definitions of infertility are inconsistent. The most generally accepted concepts include an inability to conceive after “12 months of unprotected intercourse,” inability to conceive after “12 months of attempting pregnancy” or simply “visiting a doctor for help getting pregnant” (Jacobson et al., 2018). Approximately 80% of reproductive-aged women attempting to get pregnant will do so within one year. The prevalence of infertility is approximately 11 to 13% in women (Datta et al., 2016). The main mechanisms of infertility are ovulatory disorders, tubal disorders and disorders of semen quality. A representative British study reported that 25% of couples seeking help for infertility had an ovulatory disorder, 18% had a tubal disorder, and 25% had a problem related to semen quality. No etiology was identified in 38% of the couples (Wilkes et al., 2009). In a study based at an infertility service in Israel, 37% of couples had an ovulatory disorder, 18% had a tubal disorder, 45% had a semen quality problem, and 18% of couples had more than one diagnosis. In the remaining 21% of couples, no explanation was identified (Farhi and Ben-Haroush, 2011).

When discussing these epidemiological data and their relationship to psychological factors, it is important to disengage oneself from the dichotomy of explained and unexplained infertility and not to automatically equate unexplained infertility with “psychogenic” infertility. Hypothalamic amenorrhea (HA) and polycystic ovary syndrome (PCOS) both have well-characterized endocrine mechanisms. At the same time, behavioral factors play important roles in both disorders.

**Experimental studies about behavioral mechanisms in infertility**

By reviewing experimental studies examining the effects of caloric restriction and exercise, one gains insight regarding the sensitivity of the female reproductive system to behavioral factors. In one experiment, a restrictive diet providing 1000 kcal per day resulted in significant alterations of the pulsatile secretion of luteinizing hormone (LH) followed by alterations of progesterone secretion during the luteal phase (Pirke et al., 1989). Studies in athletes show that when nutritionally derived energy falls below a certain threshold and is then combined with high energy expendi-
ture, there is an increased risk of menstrual dysfunction (Loucks et al., 2011; Williams et al., 2015; Fahrenholtz et al., 2018). In another study, over-feeding and short-term weight gain induced alterations of LH-secretion that are similar to those observed in obesity and PCOS (van Leckwyck et al., 2016).

The emotional response of women with infertility – cross-sectional studies

One out of every five women experience a major depressive episode during their lifetime (Bromet et al., 2011). Young women of reproductive age, in particular, have a high risk for depression. The point prevalence of major depressive episodes is around 6% in women (Ferrari et al., 2013). This suggests the a priori risk percentage for suffering from depressive symptoms for women with infertility. Numerous studies have examined depression and anxiety symptoms in women with newly diagnosed infertility. Most but not all studies reported an increased symptom load where 10 to 50% of subjects reported mild to moderate depression symptoms (review in (Williams et al., 2007a)). Severe depression symptoms also predict infertility-related distress (Peterson et al., 2014). Depression and anxiety in women with infertility are both associated with higher rates of problematic personality traits like neuroticism (Volgsten et al., 2010).

The results from these studies are difficult to interpret. Reporting more sadness and anxiety cannot automatically be considered pathological as it may be part of a normal adaptive emotional reaction. Cross-sectional studies do not allow for establishing causality. Depressive symptomatology may be the consequence of infertility and the struggle with its consequences and treatment. It may also represent causal factors. The study quality is usually low. Most studies allowed subjects to self-rate their symptoms, and this makes discriminating between clinical and subclinical symptoms difficult.

Only a small number of studies used standardized diagnostic interviews in unselected populations. A Taiwanese study found major depression in 17% of 112 women, dysthymia in 10% and generalized anxiety disorder in 23% (Chen et al., 2004). A representative study from Finland, based on a sample of 2291 individuals between the ages of 30 and 44, found an increased risk for dysthymia (odds ratio 3.4) and anxiety disorder (odds ratio 2.6) in women who had experienced infertility (Klemetti et al., 2010).

Several population-based studies yield important insights. A cohort study from Denmark comprising 51,221 women seeking infertility treatment between 1973 and 1998 reported an increased rate of suicide in the subgroup of women who remained childless after their fertility evaluation (hazard ratio 2.53) (Kjaer et al., 2011). A similar register-based cohort study from Denmark used data from 98,320 women evaluated for fertility problems between 1973 and 2008. The outcome measure used was hospitalization for a mental disorder. Overall, the risk was slightly increased (hazard ratio 1.17), yet this did not apply to affective disorders (Baldur-Felskov et al., 2013). A Danish study that included outpatient treatment reported an increased risk of unipolar depression in women who had received assisted reproductive treatment and achieved a first live birth. The risk was highest within the initial 42 days following delivery (Sejbaek et al., 2015). A Swedish cohort study assessing 520 women, aged 20 to 23, found an increased risk of depressive symptoms, obsessive–compulsive symptoms and somatization symptoms after in vitro fertilization (IVF) treatment, albeit there was a
small effect size (Vikstrom et al., 2015). A further study included all women treated for infertility in Western Australia between 1982 and 2002. The paper reported a lower admission rate into mental health hospitals compared to the general population. The authors explained this result by the healthy cohort effect (Stewart et al., 2015).

The influence of emotional distress on the treatment of infertility

A high number of studies have examined whether the influence of stress, anxiety and depression is associated with less favorable outcomes of assisted reproductive technology (ART). Most but not all studies report decreased pregnancy rates for those afflicted (for review, see Williams et al., 2007a; Karlidere et al., 2008; Gurhan et al., 2009; Pasch et al., 2012; Haimovici et al., 2018). A meta-analysis shows that assisted reproductive technology failure is associated with increased depression and anxiety. Correspondingly, depression decreased with successful treatment (Milazzo et al., 2016).

Fecundity and mental disorders

A Norwegian study compared the number of children from more than 30,000 married women who had received inpatient treatment due to a mental disorder to a reference population and found no significant differences (Odegard, 1980). A more recent study used Swedish register data. The study reported no decrease in the number of children for women with life-time depression; small decreases in fecundity (fertility ratio between 0.70 and 0.95) in men with bipolar disorder, women with bipolar disorder, men with depression, women with anorexia nervosa, and men and women with substance abuse and a strong reduction of fecundity (FR between 0.2 and 0.5) in men and women with schizophrenia, men and women with autism and men with anorexia nervosa (Power et al., 2012).

Studies examining specific aspects of mental disorders and infertility

Depression and infertility

A prospective study performed in the United States, at a special service for patients with affective disorders, found lower fertility in both men and women with depression when compared to population norms (Baron et al., 1982). A population-based study compared 332 women with a history of major depression to a comparison group of 664 perimenopausal women. Two findings in the depression-affected group were a significantly lower mean number of children and a higher percentage of women without children. Furthermore, the depressed group experienced menopause at an earlier age than the comparison group. (Harlow et al., 2003). A prospective population-based study compared the fertility risk in a group of 58 women who reported a history of depressive symptoms to a comparison group of 281 women who identified that women who had experienced depressive symptoms were 70% more likely to encounter infertility, even after adjusting for demographic and lifestyle factors (Lapane et al., 1995). Depressed adolescent women reported having menarche at a later age as well as experiencing amenorrhea and oligomenorrhea more frequently than population norms. (Bisaga et al., 2002). A prospective study included 174 women during the course of their fertility treatments. At baseline, 24% of the women suffered from depressive symptoms in the clinical range. Over the course of the 18-month study period, however, 39% met the criteria for major depressive disorder (Holley et al., 2015). Depressed women were also less likely to seek medical treatment for infertility (Her-
Eating disorders and infertility

Approximately 17 to 44% of women seeking medical care for infertility suffer from a clinical or subclinical eating disorder (Stewart et al., 1990; Resch et al., 1999; Andersen and Ryan, 2009; Freizinger et al., 2010; Bruneau et al., 2017). In contrast, a Danish cohort study of women who were treated using assisted reproductive technology found a similarly low rate of hospitalization due to eating disorders as that found in the general population (Assens et al., 2015). Although an Australian study involving women undergoing infertility treatment found no global difference in the rate of self-reported eating disorders, it revealed that women with an ovulatory disorder or PCOS scored higher on the eating disorder examination questionnaire (EDE-Q) (Rodino et al., 2016). Disturbance of ovarian function in women with eating disorders is not limited to women with anorexia nervosa but can also be found in women with bulimia nervosa and binge eating disorder. The extent of disturbance varies with nutrition and weight (Schweiger et al., 1992; Poyastro Pinheiro et al., 2007). It has been demonstrated that women with eating disorders often suffer from sexual dysfunction, which may contribute to infertility (Zemishlany and Weizman, 2008). Women with infertility tend not to discuss behavioral problems with their physicians (Domar et al., 2012). Women struggling with eating disorders are reported to have an increased risk for adverse perinatal events, including more miscarriages and higher rates of low-birthweight children (Koubaa et al., 2005; Micali et al., 2007). In The Generation R Study, a Dutch longitudinal birth cohort study, women with eating disorders had similar fecundity as women without psychiatric disorders. Women with lifetime bulimia nervosa underwent more infertility treat-ments, while those with lifetime anorexia nervosa had more unplanned pregnancies (Micali et al., 2014). Women with anorexia nervosa and bulimia nervosa both required more time to conceive than those without eating disorders (Easter et al., 2011). For a comprehensive review of this topic, see “Obstetric and gynecological issues in women with eating disorders” (Kimmel et al., 2016).

Hypothalamic amenorrhea

A large minority of women with infertility suffer from hypothalamic amenorrhea (HA). In this disorder, the decreased secretion of estradiol and progesterone is due to a decreased secretion of luteinizing hormone (LH). Women with HA are characteristically underweight, but even normal weight women with HA suffer from hypercortisolism and have low bone density (Lawson et al., 2009). HA patients and patients with depression both experience hypercortisolism to roughly the same extent. The concentration of corticotropin-releasing hormone (CRH) in the cerebrospinal fluid is elevated. Women with HA have a higher frequency of depressive symptoms compared to eumenorrheic women (Marcus et al., 2001; Brundu et al., 2006). Normal weight women with HA share psychopathological features with women diagnosed with anorexia nervosa (Bomba et al., 2014).

Polycystic ovary syndrome (PCOS)

Another large minority of women with infertility suffer from PCOS. Together, HA and PCOS represent the main causes of ovulatory infertility. Important signs of PCOS are ovarian cysts with anovulation, acne, hirsutism and high androgen concentrations. Women with PCOS are frequently overweight and suffer from other symptoms of the metabolic syndrome, such as hyper-
tension and type-2 diabetes. Approximately 10 to 57% of women with PCOS suffer from a depressive disorder and a further 25% from subclinical forms of depression (Tan et al., 2008; Kerchner et al., 2009; Rassi et al., 2010; Hart and Doherty, 2015). Moreover, 25 to 36% suffer from a bulimic syndrome (Morgan et al., 2008). Conversely, it has been reported that women with bulimia nervosa show ovarian alterations that hint at PCOS (Morgan et al., 2002). A large population-based cohort study from Sweden, including 24,385 women with PCOS, showed increased odds for having at least one psychiatric disorder (odds ratio 1.56); the risk was specifically increased for bulimia nervosa, schizophrenia, bipolar disorder, depressive disorders, anxiety disorders and autism spectrum disorders. The probability of attempting suicide was 40% higher than that in the general population (Cesta et al., 2016).

**Mechanistic models linking mental disorders and infertility**

**Stress**

A research group at the Oregon National Primate Research Center developed a primate model of HA. Mild psychosocial stress with exposure to an unknown social environment in combination with a metabolic stressor of a food supply reduced by 20% resulted in HA in approximately 50% of the Cynomolgus monkeys. The combination of the psychosocial stressor and the metabolic stressor was considerably more impactful than each one alone (Williams et al., 2007b).

Research in rats shows that systemic stress disrupts reproductive function by inhibiting pulsatile gonadotropin secretion. The functional unit is considered to be the neurons in the hypothalamic arcuate nucleus (specifically kisspeptin/neurokinin B/dynorphin A) and agouti-related peptide to kisspeptin signaling (Grachev et al., 2014; Padilla et al., 2017).

**Life history theory**

Organisms follow a species-specific sequence in their life, with gestation, birth, growth during childhood, sexual maturation, reproduction, aging and death being significant milestones. Life history theory assumes that this sequence is shaped by evolution and also individually calibrated by early life experiences. Adverse conditions in childhood may foster a fast life history strategy including impulsive behavior, activation of the hypothalamic-adrenal-pituitary axis, early reproduction and low investment in personal mental and physical well-being. As a matter of fact, empirical research has shown that having survived a serious medical disorder by age 10 is associated with women reproducing at an earlier age (Waynforth, 2012). Low socioeconomic status is equally associated with a lower age at first birth (Sheppard et al., 2016). Women who experienced familial adversity tend to reach sexual maturity earlier (Rickard et al., 2014). At the same time, adverse childhood conditions are also associated with increased rates of fertility difficulties and amenorrhea (Jacobs et al., 2015). Early onset of sexual activity is associated with later major depression (Goncalves et al., 2017). It may be assumed that the specific characteristics of a fast life history strategy offset part of the negative effects of stress on fecundity.

Food security, in this context, also plays a role. Food security means that each member of a household has continuous access to safe and adequate food and all have the opportunity to acquire food in an appropriate way. Food insecurity in western countries is associated with obesity, anxiety, depression, impulsive sexual behavior and adverse effects on pregnancies (Ivers and...
Psychotherapeutic interventions in women with infertility

A study in Boston randomized 184 women into the following groups: an intervention with cognitive-behavioral therapy (CBT) administered in groups, a self-help group or a waiting list control group. In the CBT arm, there was a significant reduction of depression and anxiety. (Domar et al., 2000a). A total of 20 of 56 CBT patients became pregnant. A comparison between the three arms was difficult because of high attrition rates in the two other arms, but there was a trend toward higher pregnancy rates and less time to pregnancy in the CBT arm (Domar et al., 2000b). A further study in this area of research compared the effect of a CBT group intervention on the success of an IVF treatment in 143 women. In the second intervention cycle, women who received the group intervention achieved a pregnancy rate of 52%, compared to only 20% in the comparison group (Domar et al., 2011). In a study in Hong Kong, 69 women undergoing IVF treatment received a mindfulness intervention. In the intervention group, there was a trend toward a higher rate of ongoing pregnancies (13/69 vs. 13/115) compared to the women in the standard treatment group (Chan et al., 2006). With only three studies reporting birth or pregnancy rates, a current Cochrane review concludes that the effects of psychological interventions for subfertile men and women are uncertain (Verkuijlen et al., 2016).

A pilot study in Atlanta randomized women with HA to either 16 sessions of CBT or to a waiting list comparison group. Ovulation occurred in 88% of the CBT group, compared to only 25% in the comparison group (Berga et al., 2003; Berga and Loucks, 2006).

Barriers to translational research in the mental disorders and infertility area

Stigma

There is a stigma associated with mental disorders. This decreases self-identification regarding mental illness (Stolzenburg et al., 2017). In this context, women seeking treatment for infertility may fear that they will be denied care if they mention issues like depression. This may correspond to the shortcomings of the provider, who may have a poor awareness that mental disorders are important factors for treating infertility. Depression may be an obstacle to seeking medical care for infertility and, in some studies, this may result in a healthy cohort effect.

Dominant treatment concepts

Worldwide, the use of assisted reproductive technology (ART) is the dominant paradigm for infertility treatment. Dominant successful concepts tend to overshadow alternatives. ART certainly cannot be replaced by behaviorally based treatments; however, psychotherapy and other behavioral interventions may, in subfertile women with mental disorders, decrease the need for infertility treatment and save economic resources.

Conclusions

The effects of mental disorders on fertility are an under-researched area. In particular, experimental or quasi-experimental studies with women (characterized by presence or absence of mental disorders) that stop a method of contraception, are lacking.

Most available data support the assumption that an increased risk for infertility exists in women with mental disorders. Unfortunate-
ly, the data are inconsistent and are characterized by high degrees of selection bias. The best supported assumption is a relationship between depressive disorders and ovulatory dysfunction in hypothalamic amenorrhea and polycystic ovary syndrome.

Depression and anxiety negatively affect the outcome of assisted reproductive technology.

Basic research in primates and rodents provides mechanistic models for the genesis of hypothalamic amenorrhea through stress and nutritional factors. There is a considerable overlap between the neuroendocrine alterations described in depressed patients and alterations seen in these experimental models.

Life history theory provides a framework to understand how inadequate nutrition and high stress precipitate negative effects on fertility that can be partially offset by a fast life history strategy. This strategy may result in absent or only slight reductions in lifetime fecundity in affected populations.

Pilot studies on cognitive-behavioral interventions are promising, yet the efficacy of psychotherapeutic and other behavioral interventions in women with subfertility cannot be evaluated determinately because of the absence of an adequate body of research. Psychotherapy and other behavioral interventions in subfertile women with mental disorders may decrease the need for infertility treatment, save economic resources and substantially increase the odds of pregnancy in women with infertility.

References


23, 2064-2071.


