Mood disorders and fertility in women: a critical review of the literature and implications for future research

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A medline literature review of fertility and mood disorder articles published since 1980 was performed in order to critically review the literature regarding a relationship between mood disorders, fertility and infertility treatment. Previous studies suggest that mood disorders, both in the bipolar and unipolar spectrum, may be associated with decreased fertility rates. Most studies report that women seeking treatment for infertility have an increased rate of depressive symptoms and possibly major depression (none showed evaluated mood elevations). Many, but not all, studies found that depressive symptoms may decrease the success rate of fertility treatment. Treatments for infertility may independently influence mood through their effects on estrogen and progesterone, which have been shown to influence mood through their actions on serotonin. Studies are limited in scope and confounding variables are many, limiting the strength of the results. In conclusion, a range of existing studies suggests that fertility and mood disorders are related in a complex way. Future studies should use clinical interviews and standardized and validated measures to confirm the diagnosis of mood disorders and control for the variables of medication treatment, desire for children, frequency of sexual intercourse, age, FSH levels, menstrual cycle regularity in assessing an interrelationship between mood disorders and fertility.

Keywords: mood disorders; infertility; fertility; women; menstrual cycle

Introduction

Women are at their greatest lifetime risk for mood disorders during their childbearing years (Weissman and Olfson, 1995). Mood, or affective, disorders include unipolar depression and bipolar disorder (American Psychiatric Association, 2000). The lifetime prevalence of major depression is 16.6% and bipolar disorder 3.9%. Adult women are at significantly greater risk, up to one and a half times that of men, of having a mood disorder (Maciejewski et al., 2001; Kessler et al., 2005). Infertility, clinically defined as the inability to conceive a child within one year, is also a common problem, affecting an estimated 5–10% of women (Abma et al., 1997). The question of whether mood disorders influence or contribute to infertility in women is an area in need of further research.

The goals of this paper are to critically review the literature regarding the relationship between mood disorders and fertility in women and identify variables that need further investigation. We examine primary studies found in a Pub-Med literature search on women, fertility status and mood from 1980 onwards. We used the following key words in combination: depression, depressive disorder, major depression, depressive episode, mania, bipolar disorder, psychiatric disorders, or mood disorder, with menstrual cycle, infertility, fertility, conception, in vitro fertilization (IVF), menstrual cycle, functional hypothalamic amenorrhea, hypothalamic-pituitary-gonadal axis (HPG) or pregnancy.

Several reviews address stress, depressive symptoms and anxiety in relation to fertility (Edelmann and Connolly, 1986; Wright et al., 1989; Golombok, 1997; Greil, 1997). However, in this review, we focus our analysis on clearly defined mood disorders. In part one, we investigate and analyze the interrelationship of mood disorders and fertility by reviewing the literature under the following domains: studies of fertility rates in women with mood disorders, including pregnancy rates in IVF patients with major depression, and rates of mood disorders in women with the diagnosis of infertility. In part two, we provide recommendations for future research.

Part I: mood disorders and fertility

Epidemiological studies of fertility in women with the diagnosis of mood disorders

Only five studies of fertility rates in women with clearly diagnosed mood disorders have been published since 1980 (Table 1) (Odergaard, 1980; Baron et al., 1982; Calzoni et al., 1990; Jonsson, 1991, Harlow et al., 2003). Two studies were excluded, see Table 2, Lapane et al., 1995, Grodstein et al., 1993. The
Grodstein et al. only investigates fertility of women prior to the first psychiatric and major depression. This study is limited by the fact that it uses different diagnostic categories evaluated: affective disorders, bipolar disorder, delusional disorder, and non-suicide or delusional delusions. Similarly decreased fertility rates were observed for those with increased risk for ovulatory infertility, number of years married, desire and attempts to conceive, infertility evaluation or infertility treatment.

Baron et al. (1980) analyzed the number of children born prior to the first psychiatric admission of married women hospitalized for serious mental illness in Norway between 1936 and 1975. The 30 438 women evaluated had 60 916 children, and Odergard (1980) analyzed the number of children born prior to the onset of the first psychiatric episode (Odergard, 1980; Calzeroni, 1990; Harlow et al., 2003). Age, an important factor in infertility, is often not controlled (Odergard, 1980; Calzeroni, 1990; Jonsson, 1991; Harlow et al., 2003), nor are occult causes of decreased fertility evaluated, such as male factor infertility, number of years married, desire and attempts to conceive, infertility evaluation or infertility treatment.

In contrast, Baron et al.’s (1982) study of fertility rates in male and female bipolar patients controlled for several of these variables, including age of subjects, and investigated fertility rates before and after illness onset. Baron et al.’s population included 60 males and 74 females admitted to the Lithium Clinic of the New York State Psychiatric Institute between 1968 and 1974. Strict diagnostic criteria for bipolar affective disorder were used, and the age at evaluation, age at illness onset (not just the first psychiatric admission), the number and age of all children per person regardless of marital status were computed. The authors referenced a reduced fertility rate in both genders in comparison to US population norms by age. Most importantly, they found that fertility was reduced even prior to the onset of illness and stayed lower than expected in women. Men, in contrast, had an even greater reduction in fertility after the onset psychiatric illness.

Similarly decreased fertility rates were observed for those with severe mental illness in a small comparison study of patients hospitalized in 1925 (Jonsson, 1991). Irrespective of marital status, definition of fertility varies among the studies, as does the point at which fertility is evaluated, since some studies only investigate fertility before the onset of the first psychiatric episode (Odergard, 1980; Jonsson, 1991), and others after the first episode (Baron et al., 1982; Calzeroni et al., 1990; Harlow et al., 2003). Age, an important factor in infertility, is often not controlled (Odergard, 1980; Calzeroni et al., 1990; Jonsson, 1991; Harlow et al., 2003), nor are occult causes of decreased fertility evaluated, such as male factor infertility, number of years married, desire and attempts to conceive, infertility evaluation or infertility treatment.

### Table 1: Epidemiological studies of fertility rates in women with mood disorders

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Subjects selected</th>
<th>Fertility result</th>
<th>Medical cause of infertility</th>
<th>Controlled for age</th>
<th>Incidence of infertility</th>
<th>Desire for children</th>
<th>Attempts to conceive</th>
<th>Birth control</th>
<th>Medication use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calzeroni et al.</td>
<td>1990</td>
<td>112</td>
<td>Bipolar and unipolar disorder with suicide attempt or delusions</td>
<td>Decreased number of children compared to non-suicide or delusional delusions</td>
<td>Not assessed</td>
<td>No</td>
<td>Not assessed</td>
<td>Not assessed</td>
<td>Not assessed</td>
<td>Not assessed</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Jonsson</td>
<td>1991</td>
<td>17</td>
<td>Affective disorder, hospitalized</td>
<td>Decreased, 71.2% of expected fertility</td>
<td>Not assessed</td>
<td>No</td>
<td>Not assessed</td>
<td>Not assessed</td>
<td>Not assessed</td>
<td>Not assessed</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Odergard</td>
<td>1980</td>
<td>30428</td>
<td>Hospitalized for unipolar depression, bipolar disorder</td>
<td>No different than population</td>
<td>Not assessed</td>
<td>No</td>
<td>Not assessed</td>
<td>Not assessed</td>
<td>Not assessed</td>
<td>Not assessed</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Baron et al.</td>
<td>1982</td>
<td>74</td>
<td>Bipolar disorder</td>
<td>Decreased, fertility in both sexes</td>
<td>Not assessed</td>
<td>Yes</td>
<td>Not assessed</td>
<td>Not assessed</td>
<td>Not assessed</td>
<td>Not assessed</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Harlow et al.</td>
<td>2003</td>
<td>332</td>
<td>History of MDE</td>
<td>Decreased, early decline ovarian function</td>
<td>Not assessed</td>
<td>No</td>
<td>Not assessed</td>
<td>Not assessed</td>
<td>Not assessed</td>
<td>Not assessed</td>
<td>Not assessed</td>
</tr>
</tbody>
</table>

### Table 2: Excluded studies of fertility rates in women with mood disorders

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Subjects selected</th>
<th>Standardized mood assessment</th>
<th>Fertility result</th>
<th>Reasons for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lapane et al.</td>
<td>1995</td>
<td>428</td>
<td>Women with a self report of antidepressant use</td>
<td>No, mood questionnaire created by authors</td>
<td>2x as likely to self-report infertility</td>
<td>Lack of diagnostic validity, mood</td>
</tr>
<tr>
<td>Grodstein et al.</td>
<td>1993</td>
<td>5</td>
<td>Antidepressant use &gt;6 mo</td>
<td>No, none</td>
<td>Increased risk for ovulatory infertility</td>
<td>Mood not assessed</td>
</tr>
</tbody>
</table>
40 women with the diagnosis of a mood disorder had birth rates significantly less than the age matched population norm. The fertility rate of these women was 71.2% of the expected frequency. As in Baron et al.'s study, fertility was decreased in women with mood disorders even before the first psychiatric admission.

Lower rates of fertility in women with a history of major depression were also found in the Harvard study of moods and cycles, a unique prospective study of women in the transition to menopause (Harlow et al., 2003). Women with a current diagnosis or lifetime history of major depression were significantly more likely than women without to have fewer live births. Although the study reported that women with a lifetime history of major depression had higher rates of divorce, separation and widowhood, it did not report important variables regarding potential for fertility, such as number of years married, desire and attempts to conceive, infertility evaluation or infertility treatment.

Calzeroni et al., (1990) studied fertility rates of 186 male and female patients with DSMIII-R diagnosed major depression with psychotic features and compared patients with mood congruent delusions or suicidal behavior to those without. Fertility was determined only in married subjects under 45 years old and expressed as mean number of legitimate children born alive, as a percentage of childless patients and as high (more than two children) or low fertility (less than two children). Patients who had attempted suicide had significantly fewer children than that of non-Attempters (1.5 + 0.9 versus 1.9 + 1.1) and there was lower frequency of high fertility cases, despite similar rates of childless patients in the two groups. There was no significant difference between patients with and without delusions in rates of childlessness (12/99 versus 4/29) but patients without psychotic symptoms were 2.4 times more likely to show a condition of high fertility. These non-psychotic patients had a non-significant trend for an increased mean number of children, thus suggesting differential fertility within the members of this group.

To make conclusions about the fertility rate in women with mood disorders is difficult because of the variability of the studies, although the above findings are suggestive of a potential reduced fertility rate when fertility is defined as observed versus expected number of children. Two questions that do emerge from these studies are whether fertility is diminished prior to the first mood episode, and therefore may be a sign of a greater risk for later onset of a mood disorder and whether specific phenotypes of mood disorders are associated with greater reductions in fertility.

**Menstrual abnormalities in unipolar and bipolar disorders**

Depressive symptoms have been associated with changes in the menstrual cycle that may lead to reduced female fertility. Six studies are listed in Table 3 and three excluded studies in Table 4. In a large, carefully controlled cross-sectional study of adolescent girls, Bisaga et al., (2002) reported that depressive symptoms (defined as a Beck Depression Inventory >16) were associated with late menarche, secondary amenorrhea and irregular menstrual cycles. Two large cross-sectional studies of women have also reported that women with a current or past history of depression report a history of early menstrual irregularity. However, both studies are limited by recall problems inherent in retrospective diagnosis as well as a lack of control groups (Rowland et al., 2002; Harlow et al., 2004).

Joffe et al., (2006) did include a control group in a study comparing 245 women with major depression to 619 healthy controls.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Mood disorder</th>
<th>Menstrual cycle result</th>
<th>Controlled for age</th>
<th>Endocrine evaluation</th>
<th>BMI</th>
<th>Substance use</th>
<th>Hormonal contraception</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisaga et al.,</td>
<td>2002</td>
<td>2547</td>
<td>BDI depression</td>
<td>Delayed menarche, secondary amenorrhea, irregular cycles</td>
<td>13–18 selected</td>
<td>None</td>
<td>Yes</td>
<td>Assessed</td>
<td>Not reported</td>
</tr>
<tr>
<td>Harlow et al.,</td>
<td>2003</td>
<td>644</td>
<td>History of MDE</td>
<td>Early menopause</td>
<td>36–45 selected</td>
<td>None</td>
<td>Yes</td>
<td>Assessed</td>
<td>Excluded</td>
</tr>
<tr>
<td>Rowland et al.,</td>
<td>2002</td>
<td>3941</td>
<td>History of antidepressant use</td>
<td>Intermenstrual bleeding, irregular cycles and long cycles Oligomenorrhea, amenorrhea</td>
<td>21–40 selected</td>
<td>FSH, LH, estradiol</td>
<td>Yes</td>
<td>Not assessed</td>
<td>Not reported</td>
</tr>
<tr>
<td>Rasgon et al.,</td>
<td>2005</td>
<td>80</td>
<td>Bipolar disorder</td>
<td>18–45 selected</td>
<td>None</td>
<td>FSH, LH, estradiol, free testosterone, 17 alpha OH progesterone</td>
<td>Yes</td>
<td>Not assessed</td>
<td>Excluded</td>
</tr>
<tr>
<td>Rasgon et al.,</td>
<td>2003</td>
<td>17</td>
<td>Bipolar disorder</td>
<td>18–45 reported</td>
<td>None</td>
<td>No (weight)</td>
<td>Yes</td>
<td>Not assessed</td>
<td>Included</td>
</tr>
<tr>
<td>Joffe et al.,</td>
<td>2006</td>
<td>1059</td>
<td>Unipolar and bipolar depression</td>
<td>History of menstrual abnormalities: bipolar greater than unipolar or healthy women</td>
<td>None</td>
<td>None</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
and found no statistical significance between the two groups regarding history of menstrual abnormalities prior to the diagnosis and treatment of a mood disorder. However, in the 295 bipolar women in this study, a history of menstrual abnormalities was more common (34%) than in the depressed women (24.5%) or the control women (21%). Rasgon et al., (2005) also found that in women with bipolar disorder, menstrual abnormalities frequently preceded treatment with a mood stabilizer. These studies, while limited by recall bias, are intriguing because they suggest that if a higher rate of menstrual abnormalities exists in women with mood disorders, then the hypothalamic gonadal axis (HPG) may be affected by the disorder even prior to, or in conjunction with the hypothalamic adrenal axis.

Surprisingly, there are few studies which have carefully evaluated the presence of major depressive disorder in women with functional hypothalamic amenorrhea (FHA). FHA is characterized by disturbances in GnRH pulsatility and this disturbance appears to be mediated by increased cortisol, since basal ACTH and cortisol levels have been found to be higher in FHA patient compared with controls (Mezzekalski et al., 2000). In their comparison of women with FHA, women with organic amenorrhea and eumenorrheic control women, Marcus et al., (2001) found that women with FHA reported more depressive symptoms and dysfunctional attitudes than eumenorrheic women, but not significantly more than women with organic amenorrhea. Since standardized depression scales were not used, it is not clear whether the women met criteria for an affective disorder. Thus, we recommended that future studies of FHA characterize depressive phenotype, including whether patients meet criteria for the subtypes most classically associated with hypercortisolism in mood disorders, such as melancholic and psychotic depression.

**Phenotypic differences in depression and potential influence on fertility**

One mechanism by which depressive disorders may influence fertility is by the symptoms of decreased energy, libido, self-esteem, increased guilt and psychomotor retardation. Suicidal ideation also would be expected to decrease motivation for a new life and this was found in Calzeroni et al.’s study (1990).

Bipolar disorder may also influence fertility, since increased libido is a common experience during mood elevations. However, other symptoms that occur during hypomania or mania, such as an increase in behaviors that may cause self harm or injury and a decline in self-care, would not be expected to improve fertility.

Future studies should examine the relationship between fertility and specific depressive or manic phenotypes since not all patients with a mood disorder experience the same severity of symptoms that may influence fertility. Future epidemiological studies of mood disorders and fertility should attempt to assess for frequency of sexual intercourse, desire for children and presence or absence of birth control as well.

**Psychopharmacologic considerations**

**Antidepressants and fertility**

The use of psychotropic medications needs to be critically assessed in studies of fertility rates in patients with mood disorders, since several treatment medications may impact fertility. For example, the decreased libido seen with serotonin selective reuptake inhibitors (SSRIs) has not been assessed specifically in relation to fertility in mood disorders. Furthermore, these medications may affect fertility rates by potentially increasing spontaneous abortion rates. A recent meta-analysis of six cohort studies of 1534 antidepressant exposed women and 2033 non-exposed women found that exposure to antidepressants was associated with a significant increase in rates of spontaneous abortion (3.9%). No differences were found among classes of drug (Hemels et al., 2005). Klock et al.’s (2004) recent pilot study, a retrospective chart review of the IVF outcome of women taking SSRIs and women not taking SSRIs, found that 40% of women taking SSRIs had ongoing pregnancies compared with 51% not taking SSRIs. The study is unique in that it controlled for key variables that could affect fertility, and reported that there were no differences in number of oocytes fertilized, percentage of eight cell blastocysts developed or initial hCG values.

Although it is an apparently uncommon phenomenon, antidepressants have been associated with the onset of hyperprolactinemia. Hyperprolactinemia could be an independent variable that influences menstrual cycle function, and consequently fertility, in depressed women. (Emiliano and Fudge, 2004).

**Mood stabilizers and fertility**

No studies exist for the influence of the mood stabilizers, lithium, valproic acid, carbamazepine and lamotrigine, on fertility rates in

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**Table 4: Excluded studies, menstrual cycle in women with a mood disorder**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Mood disorder</th>
<th>Menstrual cycle result</th>
<th>Reason excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harlow et al.,</td>
<td>1995</td>
<td>344</td>
<td>Major depression, treated</td>
<td>Early menopause</td>
<td>Women were perimenopausal</td>
</tr>
<tr>
<td>Kemeter</td>
<td>1988</td>
<td>551</td>
<td>Geisen personality test’, depressive</td>
<td>Higher depression score correlated with intermenstrual bleeding</td>
<td>Lack of diagnostic validity, mood</td>
</tr>
<tr>
<td>Resch et al.,</td>
<td>1999</td>
<td>75</td>
<td>BDI depression</td>
<td>Depression prevalence 64% in non-organic menstrual disorder</td>
<td>Eating disorder subjects</td>
</tr>
<tr>
<td>Gendell et al.,</td>
<td>2000</td>
<td>82</td>
<td>SCID depression</td>
<td>Depression contribute to perpetuation of menstrual disturbances</td>
<td>Eating disorder subjects</td>
</tr>
</tbody>
</table>

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women with mood disorders. Several investigations have suggested that valproic acid may decrease fertility in women since it has been associated with hyperandrogenism, hyperinsulinemia and dyslipidemia and menstrual abnormalities (Morrell et al., 2003, 2005; Rasgon et al., 2004). Valproic acid is a well documented teratogen, but the impact of this medication on fertility is currently unknown (Holmes et al., 2001).

Atypical antipsychotics are increasingly used in the treatment of mood disorders, as mood stabilizers (Malhi et al., 2003), to treat mania (Perlis et al., 2006) and to augment antidepressant response (Nemeroff, 2005). These medications, especially risperidone, may increase prolactin levels in women even at low doses (Haddad and Wieck, 2004). The associated hyperprolactinemia may lead to menstrual cycle abnormalities and thereby independently influence fertility. The only existing prospective study of pregnancy outcome of women using atypical antipsychotics includes both mood and psychotic disorder patients. This study found that olanzapine, risperidone and quetiapine are not associated with an increased risk of spontaneous abortions (McKenna et al., 2005).

Rates of mood disorders in female patients with infertility

Another approach to evaluating whether mood disorders lead to decreased fertility is to review the prevalence of these disorders in infertility patients. An increased prevalence of depressive symptoms in infertility patients compared with a variety of control groups has been found in most (Link and Darling, 1986; Reading et al., 1989; Stewart et al., 1992; Domar et al., 1992, 1993; Merari et al., 1992; Thiering et al., 1993; Chiba et al., 1997; Beutel et al., 1999; Lukse et al., 1999; Oddsens et al., 1999; Matsubayashi et al., 2001; Fassino et al., 2002) but not all studies (Paulson et al., 1988; Downey et al., 1989; Connolly et al., 1992; Downey et al., 1992; Hynes et al., 1992; Beaurepaire et al., 1994; Visser et al., 1994; Bringhenti et al., 1997; Slade et al., 1997; Emery et al., 2003; Guz et al., 2003).

The differing findings regarding rates of depression result from several methodological differences and problems. Most of the studies only used questionnaires to assess psychiatric symptoms. Also, the control groups vary and include no controls (Beaurepaire et al., 1994; Yong et al., 2000; Chen et al., 2004), age matched gynecology outpatient controls (Kee et al., 2000; Fassino et al., 2002), pregnant patient controls (Matsubayashi et al., 2001; Fido and Saheed, 2004), medical patient controls (Domar et al., 1993) and population controls (Domar et al., 1992; Merari et al., 1992; Thiering et al., 1993; Oddsens et al., 1999).

Furthermore, most of these studies are cross-sectional, not prospective, and the differing rates of mood disorders may be due to the timing of the psychiatric evaluation. It is important to assess women at the beginning of their infertility evaluation and treatment process since most (Thiering et al., 1993; Beaurepaire et al., 1994; Slade et al., 1997; Chiba et al., 1997; Guerra et al., 1998; Beutel et al., 1999; Lok et al., 2002; Ramezanazdeh et al., 2004) but not all (Stewart et al., 1992; Domar et al., 1992; Kee et al., 2000; Smeen et al., 2001) studies have shown that depressive symptoms are related to duration of treatment. However, even when patients are assessed at the beginning of infertility evaluation and treatment, they may have struggled with difficulty conceiving for a long time. Thus it remains difficult to assess the relationship between the onset of the affective episode and fertility problems.

Prevalence of major depression in infertility patients

Only a few of the studies that investigate depressive symptoms in newly diagnosed infertility patients actually use diagnostically valid and reliable criteria for confirming a mood disorder (Downey et al., 1989; Fassino et al., 2002; Meller et al., 2002) and they have conflicting results. Downey et al., (1989) compared 59 women who were in the initial stages of infertility treatment to a control group of women presenting for routine gynecological care. The Schedule for Affective Disorders and Schizophrenia-Life-time Version (SADS-L) was used to diagnose major depression. Downey et al., reported no significant difference between patients and controls in rates of current or past major depressive disorder. About 8.5% of the infertility patients met criteria for a current major depressive episode, compared with 2.9% of the control women. About 32.2% of infertility patients had experienced a past episode of MDE compared with 48.6% of the controls.

In contrast, Fassino et al., (2002) did find a significant difference in Hamilton depression (Ham-D) scores between two groups of women who had been attempting pregnancy for less than 2 years and fertile controls. Despite the fact that this study used Axis I psychopathology as an exclusion criteria, both infertility groups reported a significantly higher Ham-D than controls and both groups averaged above cutoff scores for mild depression (Hamilton, 1960). Mean Ham-D scores for women with organic infertility (infertility clearly related to a medical cause) was 15.4 and for women with ‘functional’ infertility was 11.72. ‘Functional’ or unexplained infertility was carefully evaluated with a 3 month diagnostic evaluation which included gynecological and andrological clinical examination, seminal liquid evaluation, post-coital test, progesterone assay, hysterosalpingography and, in some cases, biopsy of the endometrium and laparoscopy.

Chen et al., (2004) carefully assessed psychiatric diagnoses in women with varying years since infertility diagnosis. This study used the Mini International Neuropsychiatric Interview as well as Hospital Anxiety and Depression Scale (HADS) to assess the prevalence of psychiatric disorders in 112 women consecutively presenting for infertility treatment. 26.8% of the women met criteria for a mood disorder, 17% for major depression and 9.8% for dysthymia. These results are consistent with previous questionnaire only studies which have found rates of mild to moderate clinical depression ranging from 8–54% in women diagnosed as infertile (Newton et al., 1990; Domar et al., 1992; Demyttenaere et al., 1998; Lukse et al., 1999; Matsubayashi et al., 2001; Lok et al., 2002; Anderson et al., 2003).

The influence of mood disorders on infertility treatment

Another approach to assessing whether mood disorders influence fertility is to investigate whether the presence of depression influences the outcome of infertility treatment. Although several studies report on depressive or anxiety symptoms and their relationship to IVF outcome, few studies have focused on women who met full criteria for a mood disorder. Included and excluded studies are listed in Tables 5 and 6.
(1993) used the Center for Epidemiological Studies Depression Scale (CES-D) to evaluate mood state prior to initiating an IVF cycle in 113 first time participants (inductees) and 217 repeat cycle participants (veterans). In both groups, women with major depression (defined as CES-D $\geq 16$) had lower rates of pregnancy than non-depressed subjects. However, the important variables of age, FSH, oocyte or embryo status were not assessed in this study.

Smeenk et al., (2001) did control for the variables of age, number of previous pregnancies and number of embryos transferred in their analysis of pregnancy rates in relation to mood state in 291 women undergoing the first IVF/ICSI cycle. Prior to the subject’s first IVF medication treatment, the standardized Beck Depression Inventory (BDI) and State and Trait Anxiety Inventory measures were given. Smeenk et al., (2001) found that depression had an independent and significant correlation with lower pregnancy rates; however, state anxiety had an even stronger negative correlation with pregnancy rates.

Demyttenaere et al., (1998) evaluated even more variables that may independently affect pregnancy rates, in their study of depression and coping in 98 women about to begin an IVF cycle for either male subfertility, female subfertility or combined male and female infertility. About 54.1% of the women had Zung scores higher than the cutoff score for mild depression, 19.4% for moderate depression and 2% for severe depression. A higher Zung Depression score and greater depressive coping style were associated with lower pregnancy rates. When subfertile women who became pregnant were compared with women who did not, no statistically significant differences were found between the women in terms of age, duration of infertility treatment, number of previous IVF attempts, number of injected ampules of hMG, estradiol concentrations on day 6, number of retrieved oocytes and number of mature oocytes and number of fertilized and transferred embryos.

Not all studies found depressive symptoms associated with decreased pregnancy rates, but it is important to note that these studies did not control for age, duration of infertility treatment, FSH, oocyte or embryo status. Slade et al., (1997) did not find BDI depressive symptoms at intake to predict a decrease in pregnancy rates in women seeking infertility treatment. Mild depression scores at intake were not different between women who subsequently became pregnant (26%) and women who did not become pregnant (21%). Moderately depressed women at

### Table 5: The influence of mood disorders on infertility treatment

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Mood measure</th>
<th>Fertility result of higher initial depression score</th>
<th>FSH reported</th>
<th>Embryo status</th>
<th>Controlled for age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiering et al.,</td>
<td>1993</td>
<td>330</td>
<td>CES-D</td>
<td>Lower pregnancy rate after first IVF/ET cycle</td>
<td>No</td>
<td>Not reported</td>
<td>No</td>
</tr>
<tr>
<td>Smeenk et al.,</td>
<td>2001</td>
<td>291</td>
<td>BDI</td>
<td>Lower pregnancy rate with first IVF-ICSI</td>
<td>No</td>
<td>81% transferred</td>
<td>Yes</td>
</tr>
<tr>
<td>Demyttenaere et al.,</td>
<td>1998</td>
<td>98</td>
<td>Zung depression score</td>
<td>Lower pregnancy rates in female indication for one IVF</td>
<td>No</td>
<td>87% transferred</td>
<td>Yes</td>
</tr>
<tr>
<td>Emery et al.,</td>
<td>2003</td>
<td>141</td>
<td>BDI</td>
<td>Non-significant trend to lower pregnancy rate after one IVF</td>
<td>No</td>
<td>Not reported</td>
<td>No</td>
</tr>
<tr>
<td>Mindes et al.,</td>
<td>2003</td>
<td>67</td>
<td>CES-D</td>
<td>Not related to subsequent pregnancy in 6–12 mo</td>
<td>No</td>
<td>Not Reported</td>
<td>No</td>
</tr>
<tr>
<td>Slade et al.,</td>
<td>1997</td>
<td>144</td>
<td>BDI</td>
<td>Not related to subsequent pregnancy in up to three IVF trials</td>
<td>No</td>
<td>Not Reported</td>
<td>No</td>
</tr>
<tr>
<td>Demyttenaere et al.,</td>
<td>1992</td>
<td>40</td>
<td>Zung depression score</td>
<td>Lower pregnancy rate in IVF</td>
<td>Yes</td>
<td>98% transferred</td>
<td>Yes</td>
</tr>
</tbody>
</table>

### Table 6: Excluded studies on the influence of mood disorders on infertility treatment

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Mood measure</th>
<th>Fertility result of higher depression score</th>
<th>Reason excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terzioglu</td>
<td>2001</td>
<td>30</td>
<td>BDI</td>
<td>Lower pregnancy rate in ART</td>
<td>Subjects dropped without explanation</td>
</tr>
<tr>
<td>Oddens et al.,</td>
<td>1999</td>
<td>281</td>
<td>WHQ subscale, depression</td>
<td>Higher frequency of fertility difficulties</td>
<td>Lack of diagnostic validity, mood</td>
</tr>
<tr>
<td>Demyttenaere et al.,</td>
<td>1995</td>
<td>50</td>
<td>High depressive coping</td>
<td>Longer conception time</td>
<td>Lack of diagnostic validity, mood</td>
</tr>
<tr>
<td>Van Balen et al.,</td>
<td>1993</td>
<td>108</td>
<td>Well being questionnaire</td>
<td>Greater depression in long-term infertile couples</td>
<td>Lack of diagnostic validity, mood, cross-sectional</td>
</tr>
<tr>
<td>Kee et al.,</td>
<td>2000</td>
<td>138</td>
<td>BDI, depression</td>
<td>Failed IVF resulted in greater depression</td>
<td>Mood assessed after IVF result known to woman</td>
</tr>
</tbody>
</table>
intake subsequently accounted for both 7% of the pregnancy and 7% of the non-pregnancy groups. Likewise, Mindes et al., (2003) reported no significant difference in initial depression scores (measured by the CES-D) in women with infertility problems who became pregnant and those who did not at 6–12 months follow-up. Neither study controlled for age, duration of infertility treatment, FSH, oocyte or embryo status.

Part II: Directions for future research

The relationship between affective disorders and fertility is extremely complex and a biospsychosocial multimodal approach is needed to tease out the many independent variables.

Recommendation 1: investigate the hypothalamic pituitary gonadal axis in mood disorder patients

More studies are needed examining the HPG axis in both unipolar and bipolar populations. Cortisol releasing hormone (CRH) induced propiomelanocortin peptides inhibit GnRH secretion and CRH has been found to be dysregulated in major depressive disorder (Gold and Chrousus, 2002). Only a few studies have focused exclusively on the hypothalamic pituitary gonadal axis in premenopausal women with the diagnosis of major depressive disorder (Young and Korzun, 2002). Baisher et al., (1995) reported that untreated premenopausal depressed women had higher testosterone levels than controls, but no differences in basal and GnRH stimulated LH, FSH, estradiol or progesterone levels. O’Toole et al., (1995) reported that in contrast to a sample of post-menopausal and perimenopausal patients, premenopausal depressed patients showed no differences in diurnal or nocturnal basal gonadotropin concentrations compared with non-depressed controls. Similarly, Young et al., (2000) matched 25 women with major depression to healthy controls of same age and menstrual cycle day and sampled FSH, estradiol and LH every 10 min for 12 h. No differences were found between the groups on any measures except lower mean estrogen levels in the follicular phase and a shorter half-life of LH in the depressed group.

In contrast, Meller et al., (2001) compared LH pulses in 26 women with current or past history of DSM IV diagnosed affective disorder (23 recurrent unipolar major depression and 3 bipolar II, currently depressed) and 24 control women. No women were on medications and there was no difference between groups regarding age, weight or day of LH sampling. All women were admitted for 8 h and LH was sampled every 10 min. Depressed patients showed slower frequency and decreased rhythmicity of LH pulses but no change in amplitude compared with controls. The clinical significance of these differences is currently not understood, since the study did not report whether these differences affected ovarian follicular development or ovulation. Further research should focus on comparing the HPG axis characteristics in women with major depression and infertility and euthymic women with infertility and the clinical outcomes of these differences.

Recommendation 2: investigate the psychopharmacologic effects of infertility medications

The psychopharmacologic effects of the infertility medication may be an important independent risk factor for the development of depression in infertility patients. Most studies have not controlled for this and have not clarified type and dose of medication. There are only a few studies and case reports investigating the effects of infertility medications on mood (Blenner, 1991; Williams and Casper, 1995; Choi et al., 2005). However, it makes theoretical sense that these medications may influence the development of mood disorders, since these medications acutely and dramatically alter serum levels of estrogen and progesterone, and research has shown that some women are especially vulnerable to the onset of mood disorders at times of hormonal change, such as postpartum and perimenopause (Rapkin et al., 2002; Chaudron et al., 2003).

For instance, many women report that clomiphene citrate is associated with mood changes, including irritability, emotionality, and increased symptoms of premenstrual syndrome (Blenner, 1991). In a small pilot study, Williams and Casper (1995) reported that clomiphene citrate is associated with fatigue at midcycle, at the time when the estradiol levels are highest. Future studies should investigate whether clomiphene and human menopausal gonadotropins, including menotropins (Humegon, Pergonal and Pregova) and urofolitropin (e.g. Metrodin), are associated with more mood changes in women with a history of mood lability at times of hormonal change, such as women with a history of premenstrual dysphoric disorder or bipolar disorder.

Recommendation 3: investigate rates of mood disorders in specific infertility populations

The prevalence of mood disorders in female infertility patients may be independently and differentially related to certain causes of infertility and future studies should control for this important independent variable. Since male factors, such as sperm motility problems, are a common cause of infertility, future studies that investigate the possibility of shared biological pathways between mood and infertility in women should clearly study female infertility separately. In so doing, the importance of biological versus psychological factors in depressive symptoms and disorders in female infertility can be elucidated, since the diagnosis of a fertility problem, even if male factor related, may itself independently affect mood.

Specific female infertility related disorders should be studied separately. For instance, Weiner et al., (2004) recently reported that women with polycystic ovarian syndrome (PCOS) experienced more depression than a matched control group and that the most negative mood scores were associated with higher free testosterone values. Similarly, Rasgon et al., (2003) reported a high prevalence of major depression in 32 women with PCOS and noted that depressive symptoms were related to BMI and insulin resistance. Rasgon et al., (2002) also described a case of a woman with treatment resistant major depression and PCOS whose mood disorder finally remitted once her insulin resistance and hyperandrogenism were treated with metformin and spironolactone.

Conclusions

Mood disorders and fertility in women have a complex relationship. This review of the literature suggests that mood disorders may be associated with decreased fertility rates, but the direction...
of causality is still unclear and likely variable, depending on independent factors, such as female infertility subtype, that need further investigation. Future epidemiological studies should use standardized, validated measures of major depression and bipolar disorder. Fertility should be clearly defined and infertility carefully evaluated prior to the diagnosis of 'unexplained' infertility. Studies should control for such confounding variables as birth control use, frequency and timing of sexual intercourse and desire for children. Studies investigating pregnancy outcome in depressed female infertility patients should control for comorbid anxiety disorders and stress levels, medication use, and report important variables such as FSH levels, number and quality of oocytes, number of embryos transferred and the quality of these embryos and rates of spontaneous abortion when comparing patients and controls. It is recommended that further research focus on the HPG axis function in women with mood disorders and the clinical correlates of dysregulation, such as differences in menstrual cycle characteristics in depressed and non-depressed patients or patients with bipolar disorder.

The influence of decreased fertility on mood disorders is also complex. Future studies should focus on specific variables and risk factors for the onset of a mood disorder, such as the effect of the hormonal manipulations associated with the assisted reproductive technology process on mood. Such research would provide information for not only the field of fertility but also for women's greater psychiatric health, since the subtle and complex relationship between HPG function and mood remains an important area of investigation across the female life cycle, from puberty to menopause.

References
Haddad PM, Wieck A. Antipsychotic induced hyperprolactinemia: mechanisms, clinical features and management. Drugs 2004;64:2291–2314.
Mood disorders and fertility


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