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

Katherine E. Williams[1], Wendy K. Marsh and Natalie L. Rasgon

Stanford Center for Neuroscience in Women's Helath, Department of Psychiatry and Behavioural Sciences, Stanford University and Hospitals, Stanford, CA 94305, USA

[1]Correspondence address. Tel: +1-650-723-2779; Fax: +1-650-724-3144; E-mail: elliew@stanford.edu

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 suggests 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) (Odergard, 1980; Baron *et al*., 1982; Calzeroni *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

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

Author	Year	*N*	Subjects selected	Fertility result	Medical cause of infertility	Controlled for age	Incidence of infertility	Desire for children	Attempts to conceive	Birth control use	Medication use
Calzeroni *et al*.,	1990	112	Bipolar and unipolar disorder with suicide attempt or delusions	Decreased number of children compared to non-suicide or delusional	Not assessed	No	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed
Jonsson	1991	17	Affective disorder, hospitalized	Decreased, 71.2% of expected fertility	Not assessed	No	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed
Odergard	1980	30 428	Hospitalized for unipolar depression, bipolar disorder	No different than population	Not assessed	No	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed
Baron *et al*.,	1982	74	Bipolar disorder	Decreased, fertility in both sexes	Not assessed	Yes	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed
Harlow *et al*.,	2003	332	History of MDE	Decreased, early decline ovarian function	Not assessed	No	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed

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.

Odergard (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 reported that the relative fertility, (here defined as number of children observed per 100 expected) was not statistically significantly different from the general population for patients within the diagnostic categories evaluated: affective disorders, bipolar disorder and major depression. This study is limited by the fact that it only investigates fertility of women prior to the first psychiatric admission, leaving unclear the timing of onset of the affective disorder in relationship to childbirth.

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,

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

Author	Year	*N*	Subjects selected	Standardized mood assessment	Fertility result	Reasons for exclusion
Lapane *et al*.,	1995	428	Women with a self report of antidepressant use	No, mood questionnaire created by authors	2x as likely to self-report infertility	Lack of diagnostic validity, mood
Grodstein *et al*.,	1993	5	Antidepressant use >6 mo	No, none	Increased risk for ovulatory infertility	Mood not assessed

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 3: Menstrual cycle characteristics in women with a mood disorder diagnosis

Author	Year	*N*	Mood disorder	Menstrual cycle result	Controlled for age	Endocrine evaluation	BMI	Substance use	Hormonal contraception
Bisaga *et al*.,	2002	2547	BDI depression	Delayed menarche, secondary amenorrha, irregular cycles	13–18 selected	None	Yes	Assessed	Not reported
Harlow *et al*.,	2003	644	History of MDE	Early menopause	36–45 selected	FSH, LH, estradiol	Yes	Not assessed	Excluded
Rowland *et al*.,	2002	3941	History of antidepressant use	Intermenstrual bleeding, irregular cycles and long cycles	21–40 selected	None	Yes	Not assessed	Not reported
Rasgon *et al*.,	2005	80	Bipolar disorder	Oligomenorrhea, amenorrhea	18–45 selected	FSH, LH, estradiol, free testos-terone, 17 alpha OH progesterone	Yes	Not assessed	Excluded
Rasgon *et al*.,	2003	17	Bipolar disorder	Long menstrual cycles	18–45 reported	None	No (weight)	Not assessed	Included
Joffe *et al*.,	2006	1059	Unipolar and bipolar depression	History of menstrual abnormalities: bipolar greater than unipolar or healthy women	Bipolar 18–45, Unipolar and healthy 36–45	None	Yes	Not Assessed	Not reported

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

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

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 (Meczekalski *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 hypercortisolemia 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 ooctyes fertilized, percentage of eight cell blastocystes 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

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; Oddens *et al*., 1999; Matsubyashi *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; Beuarepaire *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 (Beuarepaire *et al*., 1994; Yong *et al*., 2000; Chen *et al*., 2004), age matched gynecology out patient 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; Oddens *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; Ramezanzadeh *et al*., 2004) but not all (Stewart *et al*., 1992; Domar *et al*., 1992; Kee *et al*., 2000; Smeenk *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 an 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. Thiering *et al*.,

Table 5: The influence of mood disorders on infertility treatment

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

(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 $>$ 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 a 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, number of previous IVF attempts, number of injected ampules of hMG, estradiol concentrations on day 6, number of retrieved ooctyes and number of mature oocytes and number of fertilized and transferred embryos.

Not all studies found depressive symptoms associated with decreased pregnancy rates, but 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 6: Excluded studies on the influence of mood disorders on infertility treatment

Author	Year	*N*	Mood measure	Fertility result of higher depression score	Reason excluded
Terzioglu	2001	30	BDI	Lower pregnancy rate in ART	Subjects dropped without explanation
Oddens *et al*.,	1999	281	WHQ subscale, depression	Higher frequency of fertility difficulties	Lack of diagnostic validity, mood
Demyttenaere *et al*.,	1995	50	High depressive coping	Longer conception time	Lack of diagnostic validity, mood
Van Balen *et al*.,	1993	108	Well being questionnaire	Greater depression in long-term infertile couples	Lack of diagnostic validity, mood, cross-sectional
Kee *et al*.,	2000	138	BDI, depression	Failed IVF resulted in greater depression	Mood assessed after IVF result known to woman

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. Similiarly, 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 urofollotropin (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 problems, 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 ooctyes, 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.

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