Epidemiology of Depression Throughout the Female Life Cycle

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Women are at an increased risk for first onset of major depression from early adolescence until their mid-50s and have a lifetime rate of major depression 1.7 to 2.7 times greater than that for men. There is accumulating evidence that certain reproductive-related hormonal changes place women at increased risk for depression. For example, puberty marks the beginning of increased risk for depression in women. Most women report physical or emotional symptoms premenstrually, with some severe enough to be diagnosed as premenstrual dysphoric disorder. While pregnancy does not increase the risk for depression, women with past histories of depression are at risk for recurrent episodes or relapse if antidepressant medications are discontinued. Hormonal changes during the postpartum period also increase the incidence of depression. Similarly, women transitioning through perimenopause, particularly those with past psychiatric histories, report depressive symptoms. Prophylaxis and treatment to minimize severity in cases of recurrence are discussed in the article, using reproductive transitional events as markers. *(J Clin Psychiatry 2002;63[suppl 7]:9–15)*

According to a comprehensive landmark study authorized and conducted by the World Health Organization and the Harvard School of Public Health, unipolar depression is the leading cause of medical disability throughout the world.[1] Depression affects 51 million people worldwide and is responsible for more than 1 in every 10 years of life lived with disability. Results of the same study revealed that in 1990 the leading cause of disease disability in women of childbearing age (15–44 years) was unipolar major depression.

LIFETIME RISK AND PREVALENCE FOR MAJOR DEPRESSION

Women are at significantly increased risk for first onset of major depression from early adolescence until their mid-50s.[2,3] Two large-scale community-based surveys of psychiatric disorders in the United States have confirmed that the lifetime rate of major depression is 1.7 to 2.7 times greater for women than for men.[3,4] According to the National Comorbidity Survey (NCS) of men and women aged 15 to 54 years, the lifetime prevalence of unipolar depression in women is 21.3% as compared with 12.7% in men.[3] Data from the Epidemiologic Catchment Area study, completed in the mid-1980s, confirmed higher prevalence rates for depression in women in every adult age group, including the elderly.[5,6] The consistent elevation in lifetime rates for depression in women is also true internationally, although the magnitude of the sex difference ranges from 1.6:1 in Taiwan to 3.5:1 in Germany.[5,7] Nevertheless, some data suggest that the increased prevalence of depression in women may not be true for all ethnic groups. Thus, although the rates of major depression for Jewish women are similar to those for women in other ethnic groups, the rates of major depression in Jewish men are higher than in Catholic or Protestant men and higher than in all non-Jewish men combined.[8] As a result, the prevalence of major depression is equal for Jewish men and women. Notably, the same study found relatively low rates of alcohol abuse/dependence in Jewish women and an inverse association between alcohol abuse/dependence and major depression.

The data on gender-specific issues related to chronicity and recurrence of depression are conflicting. Some studies[3,4,9,10] suggest no overall gender differences in chronicity or recurrence of depression. Others[11–15] report that women are at risk for chronic and recurrent depressive illness. In a longitudinal prospective follow-up study[16] of 485 subjects (mean age = 39.6 years) with a past history of depression, female sex was a significant predictor of recurrence. One analysis of NCS data concluded that women between the ages of 45 and 54 years (the upper limit of the ages studied in the survey) were more likely than age-matched men to have recurrent episodes of depression.[17] Thus, it is possible

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Table 1. Female-Specific Characteristics of Depression in Women

Women with major depression are more likely than men to
Have atypical symptoms (mood reactivity, hypersomnia, hyperphagia, leaden paralysis, rejection sensitivity)
Report more symptoms
Have a seasonal pattern of depression
Experience comorbid anxiety
Have a family history of psychiatric disorders
Attempt suicide
Have failed suicide attempts
Report recent stressful life events
Develop depression after a major stressor
Become depressed in response to sex-related hormonal changes

Table 2. Current Theories on Factors Contributing to the Preponderance of Depression in Women

Developmental: history of poor prepubertal attachments with significant others
Traumatic history:
Personal history of traumatic losses and events (remote and recent)
History of traumatic events affecting significant others
Genetic loading: family history of affective disorders, other psychiatric disorders
Temperament (eg, anxious, inhibited)
Negative self-image
Hormonal changes: effect on mood in vulnerable women
Puberty (effect of pubertal status, timing, age at puberty)
Premenstrual hormonal changes
Pregnancy (not a risk, but not protective)
Postpartum
Postmiscarriage
Perimenopause

that an increased risk of first onset of major depression in young and middle-aged women and a female-specific increased risk of recurrence contribute to the increased prevalence of major depression in women.

GENDER-SPECIFIC DIFFERENCES IN PRESENTATION AND COURSE OF DEPRESSION

There are important differences in the presentation and symptomatology of depression in women and men (Table 1). Women are more likely than men to suffer from atypical depression, characterized by mood reactivity.[18] Depressed women are more likely to report a greater number of symptoms than depressed men.[19] Furthermore, seasonal affective disorder is 4 to 6 times more prevalent in women than in men.[18,20] Female outpatients with major depression are more likely than men to have comorbid anxiety disorders and family histories of psychiatric disorders.[21] Whereas women are 3 times more likely than men to attempt suicide in their lifetimes, men are more likely to complete suicide.[4]

A number of exogenous stressors and hormonal triggers have been postulated to more likely mediate depression in women than in men.[10] Not only are women more likely than men to report a stressful life event in the 6 months prior to a major depression,[22,23] it may be that women are more sensitive to developing depression after a major life stressor.[24] There is accumulating evidence that certain reproductive-related hormonal changes place women at increased risk for depression.[25] Thus, depressive symptoms, or major depression, may be precipitated premenstrually,[26] after delivery,[27] and perimenopausally.[28,29]

In a report on depressive symptoms in 170 outpatients diagnosed with major depression,[30] depressed women were more likely than depressed men to report appetite increase, weight gain, and carbohydrate craving. Furthermore, depressed male outpatients tended to report more social and occupational disturbance than depressed female outpatients. A recent prospective study by Kornstein et al.[31] of 635 male and female outpatients with chronic depression affirmed the 2:1 prevalence ratio of depression in general population studies and further characterized the presentation and course of chronic unipolar depression. Women tended to have a younger age at onset of depression, a greater family history of affective disorder, and greater reporting of symptoms. Data from this study revealed that female subjects displayed poorer social adjustment and quality of life than male subjects. Women reported more difficulties with marital relationships, while men reported more impairment in their work environments. Women with chronic depression exhibited greater sleep difficulties, psychomotor retardation, and more somatic symptoms such as somatic pain and lack of vitality. Additional prospective studies are needed to further refine and delineate gender-specific differences among subjects with new-onset, chronic, and recurrent major depression. Nevertheless, it is clear that major depressive illness has serious negative consequences in women, who tend to express their dysfunction with severe mood impairment, neurovegetative changes, somatic symptoms, and interpersonal difficulties.

THE EMERGENCE OF THE DEPRESSION GENDER GAP AT PUBERTY

A number of theories have been suggested to explain why there is a sudden rise in the rate of depression in girls at puberty, eventually leading to a female-to-male ratio of approximately 2:1 (Table 2). Kendler et al.[32] evaluated risk factors for depression in a population-based sample of female twins and concluded that the risk for major depression may result from a complex interaction of traumatic experiences, genetic factors, a previous history of major depression, and temperament ("neuroticism"). That negative life events contribute to the preponderance of depression in women has been suggested by a number of authors.[32–35] Negative events assessed included distal traumas, such as parental loss, as well as proximal events such as divorce, separation, marital discord, severe illness or injury, robbery or assault, loss of a job, or death or serious illness of a close relative. Recent stressful events in

particular appear to represent a very powerful risk factor for female major depression.[32]

It has been hypothesized that other factors such as pubertal status, pubertal timing, age, and hormonal mechanisms may increase the depressive vulnerability of women to negative life events.[34,36–38] A recent prospective epidemiologic study by Angold et al.[34] has shown that pubertal stage (Tanner III) rather than chronological age is correlated with the increased prevalence of depression in young adolescent girls. Stattin and Magnusson[36] observed that difficulties with self-image and temperament in girls who develop sexually earlier than their peers may provoke the emergence of adolescent depression.

A recent report by Cyranowski et al.[38] proposed that it is the interrelationship between new, hormonally driven needs for affiliation, difficulties with the transition to adolescence, and negative life events that predisposes a subset of women to the development of depression. Pubertal hormonal changes, particularly increases in oxytocin, may drive an increase in the need for close emotional communication, intimacy, and responsiveness in adolescent girls. Thus, it may be that at puberty, biologically and socially mediated events and experiences prime affiliative behavior in girls. The Cyranowski group further postulated that adolescent girls who lack healthy parental attachments tend to have an anxious or inhibited temperament, and those that failed to develop good coping skills are at increased risk for depression. The risk is particularly great when such girls are faced with the challenges of new and multiple attachment systems in the context of hormonal fluctuations.[38]

In a recent prospective study[39] of male and female juvenile twins, genetic loading appeared to be positively associated with negative life events in pubertal girls. The authors suggest that a combination of genetic loading and negative life events may at least partially account for the emergence of female depression in pubertal girls.[39] They also noted that the genetic risk for depression in adolescent girls was attributable to a genetic predisposition to experiencing negative life events as particularly stressful.

DEPRESSION AS A FUNCTION OF REPRODUCTIVE-RELATED TRANSITIONS IN WOMEN

Premenstrual Disorders

Whereas up to 80% of women of childbearing age who actively menstruate affirm physical or emotional symptoms premenstrually,[40,41] approximately 3% to 8% of women experience symptoms so severe that they meet DSM-IV criteria for premenstrual dysphoric disorder (PMDD) (Table 3).[42] PMDD is characterized by recurrent physical and emotional symptoms that occur only during the late luteal phase of the menstrual cycle, remit within a few days after menstruation, and must not be due solely to an exacerbation of another disorder.[43] Some form of premenstrual syndrome comprising emotional and somatic symptoms has been reported across a number of cultures. Nevertheless, it appears that women from the United States are more likely to complain of premenstrual affective symptoms, whereas women from India and China tend to more frequently report somatic symptoms.[44] The symptoms of PMDD are so severe that patients with the disorder experience disruption in their relationships and impairment in work productivity.[45–47] The likelihood of past major depressive disorder in women with PMDD is reported to be 30% to 70%,[45] and 29% of PMDD patients with children have experienced postpartum depression.[48] Women with PMDD are also at increased risk for the development of subsequent major depression.[49] It is also true that some women with primary mood disorders such as major depressive disorder or bipolar disorder (especially rapid-cycling bipolar disorder) experience an exacerbation of their symptoms during the late luteal phase.[45] To substantiate the diagnosis of PMDD, symptoms must be present solely during the luteal phase as noted by at least 2 prospective daily ratings. The high degree of PMDD comorbidity with other psychiatric disorders along with the increased risk for women with PMDD to experience a reproductive-related psychiatric disorder highlights the importance of careful screening and diagnosis of women for premenstrual depressive, angry, irritable, or physical symptoms.

Pregnancy and Depression

Although rates of major depression are similar in pregnant and nonpregnant women, about 20% of women affirm depressive symptoms during pregnancy.[27,50] The risk for depression increases during pregnancy with prior history of depression,[51] maternal youth,[52] maternal isolation, insufficient social support, marital discord, ambivalence about the pregnancy,[53] and a greater number of children.[54] Since depressed patients tend to neglect themselves, a depressive episode during pregnancy increases the risk for suicide and poor self-care, which may compromise the health of the developing fetus.[55] Depressed women are at increased risk for preterm deliveries and babies small for gestational age.[56] Uncontrolled depression during pregnancy triples the risk for depression in the postpartum.[56]

As in nongravid women, premature discontinuation of antidepressant medication during the acute, continuous, or maintenance phases of treatment in pregnant women may precipitate a relapse or recurrence of depression. In nongravid populations, although 22% or fewer of patients on continuation medication therapy suffer relapse, 40% to 60% of patients who have their medication discontinued over the same time period experience relapses.[57–59] Addressing a similar issue in pregnant women, Cohen[60] found that 75% of women with recurrent major depression who discontinued their antidepressants at the time of pregnancy relapsed during the index pregnancy, and of these, 69% relapsed within the first trimester. General recommendations for the

Table 3. Depression as a Function of Reproductive-Related Transitions in Women

Condition	Reproductive Transition	Frequency	Risks
Premenstrual syndrome	Luteal phase of the menstrual cycle	Up to 80% of naturally menstruating women	None known
Premenstrual dysphoric disorder	Luteal phase of the menstrual cycle	3%–8% of naturally menstruating women	History of major depression, postpartum depression, other affective disorders
Depression in pregnancy	Antepartum months	No altered risks for major depression as compared with nonchildbearing controls. 20% of pregnant women may have minor depressive symptoms	Prior history of depression, maternal youth, insufficient social support, marital discord, ambivalence about the pregnancy, greater number of children, premature discontinuation of antidepressant treatment
Postpartum "blues"	First 2 postpartum weeks	50%–80% of postpartum women	None known
Postpartum depression	First postpartum month; some suggest up to first 3 postpartum months	10%–22% of postpartum women	Prior personal or family history of depression, past postpartum depression, depression during pregnancy, marital dysfunction, poor primary supports, negative life events during pregnancy
Postpartum psychosis	First postpartum month, especially first 2 postpartum weeks	0.1% of postpartum women	Personal history of bipolar disorder, prior postpartum psychosis, family history of bipolar disorder, primiparity, psychosocial stressors
Perimenopausal depression	5–7 years prior to menopause	Increased minor depressive symptoms; exact frequency unknown. No increased frequency of new-onset major depression. Unspecified increased frequency of perimenopausal major depression in women with prior depressive histories	Past history of major depression, lengthy and severe vasomotor perimenopausal symptoms

treatment of depression include the proviso that antidepressant treatment should continue for at least 4 to 6 months after remission has begun in order to effectively prevent depressive relapse.[57–59] Particular caution should be exercised in the first 8 weeks after medication discontinuation, as it is during this time interval that risk for relapse is highest.[59] Since pregnancy does not protect against new-onset, relapsing, or recurrent depression, the same recommendations may well apply to women who are being treated for depression with antidepressants and become pregnant. If pharmacotherapy is considered during pregnancy, the risk to the mother and fetus of antidepressant discontinuation and subsequent depression must be carefully weighed against the risks of antidepressant use during pregnancy. As more reassuring data accumulate with regard to the safety of many antidepressants during pregnancy, consideration should be given to agents with an established safety profile for both pregnant mother and fetus.

Postpartum Mood Disorders

Fifty percent to 80% of women experience "postpartum blues," a condition characterized by no more than 2 weeks of mild depressive symptoms of mood instability, tearfulness, anxiety, and insomnia.[61,62] Rates of major depression with postpartum onset ("postpartum depression") have been reported to range from 10% to 22% of women.[63–65] The 6-month prevalence of postpartum depression is similar to that in the general female population, approximately 10%. Nevertheless, there is a 3-fold increase in the incidence of depression within the first 5 postpartum weeks and a 7-fold increase in the rate of psychiatric hospital admissions in the first postpartum month.[66,67] Postpartum depression arises within the first postpartum month and has a generally similar clinical profile to major depressive disorder occurring at other times, although patients with postpartum depression typically are markedly anxious and tend to ruminate over the health and well-being of their babies.[68]

Risk factors for postpartum depression include a prior personal or family history of depression, past postpartum depression, depressive symptoms during the index pregnancy, marital dysfunction, inadequate primary supports, and negative life events during pregnancy.[68–71] Up to 30% of women who experience postpartum depression have had a past history of depression,[50] and a prior postpartum depression increases the risk to 50% for a subsequent episode.[72] Although it is unclear if postpartum women without a prior history of mood disorders are at increased risk for major depression, they do appear to have higher rates of depressive symptomatology.[73]

The etiology of postpartum depression is unknown, but is probably associated with hormonal changes occurring during the acute postpartum period. It has been suggested

that the rapid and steep decline in estrogen levels after delivery may precipitate depression in vulnerable women.[74] Although an increase in postpartum hypothyroidism and thryoiditis[75–77] may account for some postpartum depression, thyroid dysfunction is not believed to explain most cases.

Postpartum psychosis, thought to be a variant of bipolar disorder, is rare and occurs in approximately 0.1% of all postpartum women.[68] Onset is typically early and rapid, occurring within the first 3 postpartum days. In a study[78] of 86 cases of postpartum psychosis, almost 80% occurred following a first childbirth and within the first 2 weeks of delivery. Rapidly waxing and waning mood swings and psychotic symptoms characterize the disorder. Auditory hallucinations and paranoia are prominent. Patients require aggressive treatment and careful supervision (almost always in an inpatient setting), as there is a risk of suicide and a small, but real, risk of infanticide. Important risk factors include a personal history of bipolar disorder or postpartum psychosis.[68] Kendell et al.[67] found that more than one third of the 486 women admitted psychiatrically with postpartum psychosis in the first 3 postpartum months had prior diagnoses of bipolar disorder, whereas fewer than 5% of hospitalized subjects had been diagnosed with schizophrenia. A family history of bipolar disorder, primiparity, and psychosocial stressors also increase the risk for the disorder.

Postmiscarriage Depression

Spontaneous abortion or miscarriage involves the death of a fetus of up to 20 weeks' gestational age. Thirty-one percent of all pregnancies spontaneously abort in the first trimester; most are unrecognized because the fertilized ovum is expelled at the time of expected menstruation.[79] It has been estimated that the actual miscarriage rate is still higher, perhaps up to 50% of all pregnancies, with most losses occurring during the 2 weeks following conception.[80]

Despite the high frequency of miscarriage in the general female population, miscarriage is a distressing physiologic and psychological event in a woman's life and may be associated with depressive symptoms, anxiety, and somatization in the 6 months following fetal loss.[81,82] In a recent cohort study,[81] the 6-month incidence of depression in women who experienced fetal loss prior to 28 weeks' gestation (10.9%) was 2.5 times greater than that found in community nonpregnant control subjects. Almost three quarters of women who experienced a postmiscarriage episode of major depression became symptomatic during the month after their loss. The relative risk was higher still (5.0) for childless women than for women with children. The same study reported that 54% of women with prior histories of major depression experienced a recurrence of depression following miscarriage.

Whether length of gestation prior to fetal loss influences the likelihood of subsequent depression or other psychopathology is a matter of controversy requiring further research for resolution.[81,82] One study[83] found that women who experience fetal loss after 18 weeks' gestation and become pregnant within 1 year incur an increased risk of depression and anxiety in the third trimester of a subsequent pregnancy and at 1 year postpartum. Women who waited at least 1 year after miscarriage, however, were no more likely than control women to experience subsequent negative psychological symptoms. It may be that women who have miscarried need a year to mourn their loss, or it may be that women who have miscarried and choose to conceive sooner are more vulnerable to depression and anxiety.

The accumulating epidemiologic data on postmiscarriage negative psychological sequelae have potential implications for both prevention and treatment. Thus, it is prudent for clinicians to offer women and their partners who have sustained miscarriages the opportunity for counseling. It is also important to screen for past psychiatric history and provide particularly close follow-up of patients with prior depressive histories. Despite the fact that major depression is not generally diagnosed within 2 months following the loss of a loved one, a prolonged depression characterized by severe guilt, thoughts of death, marked functional impairment, or other signs of severe depression should be regarded as major depression.

Menopause and Depression

Natural menopause is marked by 12 consecutive months of amenorrhea in the absence of such causes as pregnancy or lactation.[84] The median age for menopause is 51 years.[85] While perimenopause is often described as the 5- to 7-year period of transition from regular ovulatory menstrual cycles to complete anovulation,[29] it is sometimes extended to incorporate the first year after menopause.[86]

Although longitudinal studies have not found that perimenopause increases the risk for new-onset major depression, perimenopause has been associated with depressive symptoms in some women.[87–93] Furthermore, while higher risks of recurrent depression extend over the age range of 15 to 54 years, the risk particularly increases within the 45- to 54-year-old age span.[17] This increased tendency for recurrence of depression in the 45- to 54-year-old cohort of women contributes to the higher prevalence of depression in women of this age bracket as compared with age-matched men.[17] In a 5-year prospective cohort study[85] of 2565 middle-aged women, depression (as defined by a Center for Epidemiological Studies Depression Scale[94] score greater than 15) was related to the length of perimenopause and resolved postmenopausally. Four cross-sectional studies also have noted increased depressive symptoms in association with perimenopause.[89–91,93] In a small study[95] of women attending a menopause clinic, those subjects with "high psychological distress" were more likely than those with "low psychological distress" to have experienced prior depression requiring antidepressant treatment, oral contraceptive dysphoria, premenstrual syndrome, postpartum blues, and postpartum depression.

The increase of depressive symptoms in some women as they transition through perimenopause may be secondary to severe and disabling vasomotor symptoms and/or estrogen depletion in response to declining ovarian function.[28] In a recent double-blind randomized study,[96] estradiol replacement ameliorated perimenopausal depression in the absence of vasomotor symptoms, supporting the possible role of perimenopausal estrogen decline as a contributing factor in the development of perimenopausal depression. Age-related changes in women can also contribute to increased vulnerability to depression. For example, changing interpersonal roles in the family, including increased caretaking responsibilities, chronic health problems, and loss of a significant other by death, divorce, or separation, often coincide with the perimenopausal years.[85,97]

CONCLUSION

Compared with men, women have increased 1-year and lifetime risks for depression throughout adulthood. Some data suggest that women are at increased risk of recurrent and chronic depression, and it may be that this is particularly true in women aged 45 to 54 years. The gender-specific increased prevalence of depression begins to emerge at puberty and is due in large part to the increased risk for first-onset depression from early adolescence to the mid-50s. Other gender-specific characteristics of depression include differences in precipitants, exacerbating factors, presentation, and course. Further rigorously controlled prospective studies are needed to refine and extend the knowledge base with regard to these differences. These data will be useful for the prevention of depression in vulnerable women and will also guide clinicians as they develop targeted treatment protocols for new-onset and recurrent depression.

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