Mood Disorders in Women: Focus on Reproductive Psychiatry in the 21st Century

Vivien K. Burt[1] and Veronica Quezada[2]
[1]Director, Women's Life Center, Neuropsychiatric Hospital at UCLA, [2]Santa Monica UCLA Medical Center, California, USA

ABSTRACT

The burden of mental illness in general, and depression in particular, has long been underestimated. One in 6 persons in the United States will, at some point, suffer from major depression.[1] Depression is second only to heart disease as a leading cause of medical disability in the U.S.[2] Women are vulnerable to mood instability at times of life-cycle related hormonal challenge (e.g., including the premenstruum, pregnancy, post-miscarriage, postpartum and perimenopause).[3] Neurobiological, genetic, and psychosocial substrates underlie the increased vulnerability for depression in women. The significant negative impact of maternal depression on maternal and child health and psychological well-being and other possible consequences of chronic depression will be reviewed.

The enormous burden of female depression on women, their children and their families has been well-documented over the past two decades. What remains is the need for serious, rigorously conducted research into effective and safe treatments for depression in women, particularly at times of reproductive transition.

Depression in Women: Reproductive Transitions as Times of Risk

Although often taken for granted, gender-specific aspects of women's health in general and women's mental health in particular, were not subjects of interest until the mid 1990's. Spurred by the NIH Revitalization Act of 1993, a mandate was established that NIH-funded clinical research must address health issues of women and minorities.[4] Women could no longer be routinely excluded from research because they "might" become pregnant. Clinical research then began to address and answer questions about how women with psychiatric illnesses might become pregnant in a way that would safeguard their health and that of their babies. Gender-specific differences in the prevalence and clinical course of depression undoubtedly stem from a variety of factors, including biological differences between women and men. Probably due in part to genetically primed alterations in mood in response to changing hormones during reproductive transitions, women are at increased risk for mood instability at puberty, during the premenstruum, the postpartum, perimenopause, following miscarriage, and in some cases

during pregnancy.[5,6,7,8,9] Female-specific hormonal and physiological differences increase the susceptibility of women to depression, and should inform treatment decisions.

Gender-specific Neural Correlates of Depression

Women and men appear to perceive and respond to social cues in gender-specific ways, possibly reflecting different neuronal processing. In a pilot study by McClure and colleagues, men exhibited a less-discriminating pattern of activation, while adult women experienced a selective activation of the orbitofrontal cortex and amygdala in response to threatening pictures.[10] This preliminary data supports other findings that negative life events contribute to the preponderance of depression in women.[11] That women may be particularly sensitive to environmentally-loaded emotional cues is further supported by twin data of Kendler, which suggests that emotionally supportive social relationships are substantially more protective against major depression for women than for men.[12] Besides the devastating social and occupational consequences of depression, there are actual physical differences in the brains of people with untreated depression. In a study of 38 healthy outpatient female subjects with histories of recurrent depression in remission, duration of past depression was inversely related to hippocampal volume, with longer periods of untreated depression correlated with lower total hippocampal volume.[13] Because women are more likely to experience first time depression beginning at puberty and because reproductive life transitions are associated with relapse and recurrent episodes, the urgency to treat depression as fully and as early as possible is of critical importance. Animal studies reveal the psychoactive effects of female hormones. In a study of ovariectomized rats which received estradiol replacement, there was increased neuronal dendritic spine density compared with rats that were not treated with estrogen. The same study showed that progesterone augmented the effect of estradiol within hours.[14] It is not surprising that periodic hormonal vicissitudes, occurring premenstrually, perimenopausally, or in the postpartum represent times of increased vulnerability to depression for some women.

Psychosocial Correlates of Depression in Women

For some women, the risk for depression is increased by major negative life events. Traumatic experiences play a significant role in the increased risk for major depression in women as compared to men. Thus, early traumas, such as parental loss, as well as more proximal events such as divorce, separation, marital discord, severe illness, assault, loss of a job, or the death or serious illness of a close relative all appear to contribute to the preponderance of depression in women.[11] As noted**,** females are much more vulnerable to a lack of social support than their male twin siblings.[12] It is not surprising that increased child-bearing responsibilities and little social support are among the factors that increase the risk for postpartum depression. Clinically, this can be seen in young mothers who have little support when pregnant and in the postpartum, leaving them to shoulder the burden of child-bearing responsibilities.[15,16]

Clinical Correlates of Depression in Women: Focus on Perinatal Depression

The magnitude of the negative impact of depression in mothers on their infants has heightened the need to detect and treat depression in new mothers. Results from a large study of Kaiser mothers, revealed that 15.4% were found to have had a depression during at least one perinatal period (39 weeks prior to pregnancy, during pregnancy, or 29 weeks following childbirth). Of those identified with depression prior to pregnancy, 56.4% were identified with depression during pregnancy. Of women with postnatal depression, 54.2% were also identified as having been depressed before or during pregnancy. Of note, although there was a reduction in the number of antidepressant prescriptions written for the pregnant depressed women, there was not a corresponding increase in the number of mental health visits for these patients. Thus, pregnant depressed women did not get needed psychiatric care. Clinicians should be alerted to the fact that if they are treating a woman who has a history of depression, there is a greater chance that she can be vulnerable to another episode, and pregnancy does not alter this reality.[17]

Thus, for women with a history of depression, pregnancy can be a period of time of difficult choices with respect to the decision of whether to remain on medication or discontinuing medication. In

comparison with the relapse rate of approximately 25% in pregnant women who choose to remain in treatment, almost 70% of women who become pregnant and discontinue their antidepressant treatment relapse, with 50% of the relapses in the first trimester, and 90% by the end of the second trimester.[9]

The dilemma for women with bipolar disorder is particularly difficult, as most of the medications used to ensure bipolar stability are teratogenic. A recent study found that almost 70% of women elected to stop their mood stabilizing treatment early in pregnancy, regardless of illness severity. Furthermore, women who discontinued their bipolar medications proximate to pregnancy more than doubled their likelihood of suffering a recurrence of at least one episode of the illness (85.5% versus 37.0%) and spent over 40% of the time during pregnancy suffering bipolar symptoms, compared with only 8.8% of the time during pregnancy for those who maintained pharmacotherapy.[18] Most recurrences were depressive or dysphoric/mixed episodes. Abrupt cessation of mood stabilizers resulted in a 50% risk of recurrence within just 2 weeks, in contrast to 22 weeks when discontinuation occurred more gradually (over at least 15 days). Because bipolar decompensation in pregnancy is often accompanied by serious morbidity both during the pregnancy and the subsequent postpartum, the decision to discontinue stabilizing medications during pregnancy must be carefully weighed against the risk for both mother and fetus/infant of medication continuation. For all women suffering from chronic, serious psychiatric illness, careful consideration should be given to pre-conception planning. The safest possible medication regimen for a fetus that ensures maternal stability should be established before pregnancy. An open and supportive therapeutic alliance is important to screen for possibly relapse requiring reassessment of the treatment regimen.

The increased risk for postpartum mood disorders has been well-documented. Data from a recent large population-based Danish study of first time parents showed that mothers (but not fathers) were at risk for psychiatric difficulties requiring intervention during the first five postpartum months. Compared to mothers who had given birth 11-12 months prior, new mothers were three times more likely to have a first onset psychiatric hospital admission in the initial 10-19 days postpartum and seven times more likely during postpartum days 20-29. Among the mothers, there was also an increased risk for psychiatric

outpatient contacts through the first 3 months after childbirth, with the highest risk occurring 10 to 19 days postpartum. The authors found that the risk for inpatient admission varied for different psychiatric disorders. Thus for unipolar depression there was an increased risk for psychiatric hospitalization through the first five months postpartum, with a peak relative risk of 3.53 during the second postpartum month. The risk for psychiatric hospitalization in bipolar women extended through the first two postpartum months, with a dramatic relative risk of approximately 23 during the first postnatal month and 6.30 during the second postpartum month.[19]

The importance of psychiatric history both prior to pregnancy and during an index pregnancy as a predictor of postpartum psychiatric well-being was addressed in a Swedish population-based linked registry study. Without previous psychiatric hospitalizations the incidence of a psychotic or bipolar episode within the first three postpartum months was 0.04% and 0.01% of first births, respectively. In women with psychiatric hospitalization, the incidence increased to 9.24% for postpartum psychotic episodes and 4.48% for bipolar episodes. Factors that increased the risk of postpartum psychotic or bipolar episodes included the length of most recent hospitalization, the recency of pre-pregnancy hospitalizations, and the number of previous hospitalizations. Further emphasizing the importance of maintaining emotional stability during pregnancy in women with chronic psychiatric conditions, more than 40% of women hospitalized during the prenatal period for a bipolar or psychotic condition were hospitalized again during the postpartum. Of note, in this study, risk for psychiatric hospitalization was highest during the first 4 weeks after delivery, a time which corresponds to the time of greatest transition for new mothers.

The first postpartum month is a time when new mothers are faced with the challenges of care-giving for their infants, are recovering from childbirth, are sleep-deprived, are often struggling with establishing a breast-feeding routine, and are adjusting to the dynamics of a growing family. Clinicians should therefore follow new mothers with psychiatric histories closely through the initial postpartum months.

The Impact of Perinatal Psychiatric Mood Disorders on the Children

In addition to the many negative effects of untreated depressive illness during pregnancy on maternal well-being, the risk for adverse neonatal outcomes include an increased incidence of premature birth, C-section, instrumental vaginal deliveries, intrauterine growth retardation, low birth weight, postnatal complications, increased levels of neonatal stress hormones cortisol and catecholamines, and neonatal inconsolability.[20-25] Neonates of depressed mothers have poorer orienting skills, decreased motor tone, lower activity levels, lower vagal tone, right EEG asymmetry, poorer orientation, reflex, excitability, and withdrawal clusters on the Brazelton Scale.[26,27,28] Other negative child outcomes include increased depression, anxiety, aggressivity, withdrawal, hyperactivity, and delay in development at one year.[29-32]

The profound impact of maternal depression on the health and well-being of children was recently documented in a multi-site study of children of mothers who were treated with medication as part of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. Children (aged 7-17 years) were assessed psychiatrically at study inception and three months by a team of blinded evaluators. Those children who were free of any psychiatric symptoms at the inception of the study and whose mothers' depression remitted with treatment remained well, while 17% of initially well children whose mothers did not remit acquired a psychiatric disorder (depressive, anxiety, or disruptive behavior disorders). Successful treatment to remission of maternal depression was associated with an 11% decrease in rates of diagnosis for their children, whereas failure to remit resulted in an 8% increase in psychiatric diagnoses in their children.[33] These results suggest that successful treatment of maternal depression has a positive effect on the mental well-being of their school-aged children. As a corollary of this data, a twenty-year follow-up study of adult offspring of depressed parents revealed that they had higher rates of depression, anxiety, substance dependence, work dysfunction, family dysfunction, and physical illness (especially cardiovascular disease) than age-matched offspring of non-depressed parents.[34]

Depression: Is there an Effect on Childbearing Potential?

The perimenopausal transition, during which ovarian function is declining, is a time of increasing vulnerability for depressive episodes, particularly among women with a history of a mood disorder or with a lengthy symptomatic perimenopause.[35] Results from a 3-year prospective study of almost 1000 premenopausal women aged 36-44 found that women with a history of depression were 1.2 times more likely to become perimenopausal and those with higher depressive scores at the study's inception were twice as likely to become perimenopausal. Furthermore, women with a lifetime history of depression had higher FSH and LH and lower estradiol levels at the time of study enrollment and during follow-up compared with women who did not have a history of depression.[36] That current and past depression may be associated with an earlier decline in ovarian function suggests that depression may have a negative effect on fertility, further underscoring the need to treat depression promptly and vigorously.

Perinatal Depression: Where Are We Now?

Almost twenty years have passed since the Office of Research on Women's Health has spurred research that has made it clear that female gender itself is a risk factor for depression, that pregnancy does not protect against mood disorders, that there is a high risk of relapse in pregnancy for mood disorders, and that maternal depression adversely affects child development. The continued societal expectation that pregnancy and the postpartum are the happiest times in a woman's life drives some mothers into isolation, such that they do not obtain the help they need to address disabling mood-related disorders. Depression is still seen by many as a character flaw rather than a serious medical illness with a potentially fatal outcome.[37] The severe physiologic and psychological challenges unique to the perinatal period demand further high quality, evidence-based research that will shed light on appropriate and effective treatment options to address these challenges.[38]

Corresponding Author: ***vkburt@aol.com***

REFERENCES

1. Davidson JRT, Meltzer-Brody SE. The under recognition and under treatment of depression: what is the breadth and depth of the problem? J Clin Psychiatr. 1999;60 (Suppl 7):24-11.
2. Michaud CM, Murray CJL, et al. Burden of disease – implications for future research. JAMA.. 2001;285:535-539.
3. Burt VK and Stein K. Chapter 39. Treatment of Women. In The American Psychiatric Textbook of Psychiatry, fifth edition, 2008. Eds. RE Hales, SC Yudofsky, and GD Gabbard, American Psychiatric Press, Inc. Wash. DC.
4. http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm Accessed on: September 15, 2008 at 4.00pm.
5. Angold A, Costello EJ, Worthman CM. Puberty and depression: the roles of age, pubertal status and pubertal timing. Psychol Med. 1998;28:51-61.
6. Gotlib IH, Whiffen VE, Mount JH, et al. Prevalence rates and demographic characteristics associated with depression in pregnancy and the postpartum. J Consult Clin Psychol. 1989;57:148:844-852.
7. Freeman EW, Sammel MD, Lin H, et al. Associations of hormones and menopausal status with depressed mood in women with no history of depression. Arch Gen Psychiatry. 2006;63:375-382.
8. Neugebauer R. Depressive symptoms at two months after miscarriage: interpreting study findings from an epidemiological versus clinical perspective. Depress Anxiety. 2003;17:152–162.
9. Cohen LS, Altshuler LL, Harlow BL, et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. JAMA. 2006; 295:499–507.
10. McClure EB, Munk CS, Nelson EE. A developmental examination of gender differences in brain engagement during evaluation of threat. Biol Psychiatr. 2004;55:1047-1055.
11. Kendler KS, Kessler RC, Neale MC, Heath AC, Eaves LJ. The prediction of major depression in women: toward an integrated etiological model. Am J Psychiatry 1993; Aug;150(8):1139-48.
12. Kendler KS, Myers J, Prescott CA. Sex differences in the relationship between social supports and risk for major depression: a longitudinal study of opposite-sex twin pairs. Am J Psychiatry. 2005;162:250-256.
13. Sheline YI, Gado MH, Kraemer HC. Untreated depression and hippocampal volume loss. Am J Psychiatry. 2003;160:1516-1518.
14. Gould E, Woolley CS, Frankfurt M, et al. Gonadal steroids regulate dendritic spine density in hippocampal pyramidal cells in adulthood. J Neuroscience. 1990;10(4):1286-91.
15. Brown GW, Moran PM. Single mothers, poverty and depression. Psychol Med 1997;27:21-33.
16. Deal LW, Holt VL. Young maternal age and depressive symptoms: Results from the 1988 National Maternal and Infant Health Survey. Am J Public Health. 1998;88:266-270.
17. Dietz PM, Williams SB, Callaghan WN, et al. Clinically identified maternal depression before, during, and after pregnancies ending in live births. Am J Psychiatry. 2007;164(10):1515-1520.
18. Viguera AC, Whitfield T, Baldessarini RJ, et al. Risk of recurrence in women with bipolar disorder during pregnancy: Prospective study of mood stabilizer discontinuation. Am J Psychiatry. 2007;164(12):1817-1824.
19. Munk-Olsen T, Lauresen TM, Pedersen CB, et al. New parents and mental disorders. A population-based register study. JAMA. 2006; 296(21):2582-2589.

20. Bonari L, Bennett H, Einarson A, et al. Risks of untreated depression during pregnancy. Can Fam Physician. 2004;50:37-9.
21. Chun TRH, Lau TK, Yip ASK, et al. Antepartum depressive symptomatology is associated with adverse obstetric and neonatal outcomes. Psychosom Med. 2001; 63:830-4.
22. Field T, Diego, M, Dieter J, et al. Depressed, withdrawn and intrusive mothers' effects on their fetuses and neonates. Inf Behav and Dev. 2001;24:27-39.
23. Hoffman S, Match MC. Depressive symptomatology during pregnancy: Evidence for an association with decreased fetal growth in pregnancies of lower social class women. Health Psychol. 2000;19:535-43.
24. Steer RA, Scholl TO, Hediger ML, et al. Self-reported depression and negative pregnancy outcomes. J Clin Pepidemio. 1992; 45:1093-99.
25. Lundy BL, Jones NA, Field T, et al. Prenatal depression effects on neonates. Infant Behav Dev. 1999;22:121-137.
26. Abrams SM, Field T, Scafidi F, et al. Newborns of depressed mothers. Infant Ment Health J. 1995;16:231-237.
27. Jones NA, Field TM, Fox NA, et al. Newborns of mothers with depressive symptoms are physiologically less developed. Infant Behav Dev. 1998;21:537-541.
28. Lundy BL, Aaron-Jones N, Field T, et al: Prenatal depression effects on neonates. Infant Behav Dev. 1999;22:119-129.
29. Lyons-Ruth K, Wolfe R, Lyubchik A. Depression and the parenting of young children: Making the case for early preventive mental health services. Harv Rev Psychiatry. 2000;8:148-153.
30. Murray L, Cooper P. Effects of postnatal depression on infant development. Arch Dis Child. 1997;77:99-101.
31. Downey G, Coyne JC. Children of depressed parents: An integrative review. Psychol Bull. 1990;108:50-76.
32. Weinberg MK, Tronick EZ. The impact of maternal psychiatric illness on infant development. J Clin Psychiatry. 1998;59(Suppl 2):53-61.
33. Weissman MM, Pilowsky DJ, Wickramaratne PJ, et al. Remissions in maternal depression and child psychopathology, a STAR*D-Child Report. JAMA. 2006;295(12):1389-1398.
34. Weisman MM, Wickramaratne P, Nomura Y, et al. Offspring of depressed parents: 20 years later. Am J Psychiatr. 2006;63:1001.
35. Freeman EW, Sammel MD, Liu L, et al. Hormones and menopausal status as predictors of depression in women in transition to menopause. Arch Gen Psychiatry. 2004;61:62–70.
36. Harlow BL, Wise LA, Otto MW, et al. Depression and its influence on reproductive endocrine and menstrual cycle markers associated with perimenopause. Arch Gen Psychiatry. 2003;60:29-36.
37. Rubinow DR. Antidepressant treatment during pregnancy: Between Scylla and Charybdis. Am J Psychiatr. 2006;163:954-5.
38. Gaynes BN, Gavin N, Melzer-Brody S, et al. Perinatal depression: Prevalence, Screening Accuracy, and Screening Outcomes. Evidence Report/Technology Assessment No. 19. (Prepared by the RTI-University of North Carolina Evidence-Based Practice Center, under Contract No 290-0200016). AHRQ Publication No. 05-E006-2. Rockville, MD: Agency for Healthcare Research and Quality. February 2005.