Depression During Pregnancy and the Puerperium

Alexis M. Llewellyn, Zachary N. Stowe, M.D., and Charles B. Nemeroff, M.D., Ph.D.

Epidemiologic studies demonstrate a twofold higher rate of depression in women than in men. The childbearing years are a time of increased risk for onset of depression in women. Pregnancy, miscarriage or pregnancy loss, infertility, and the postpartum period may challenge a woman's mental health. Virtually no life event rivals the neuroendocrine and psychosocial changes associated with pregnancy and childbirth. This paper provides a brief overview of depression during pregnancy and the postpartum period. Incidence, risk factors, and complications of depression during pregnancy and the puerperium are discussed to aid the clinician in early identification of at-risk patients. Treatment recommendations are also provided based on the available literature, clinical experience, and consideration of the possible special circumstances (i.e., breast-feeding) of this population of women.

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Major depression is twice as prevalent in women as compared to men,[1] and the childbearing years appear to be a time of increased vulnerability for the onset of mood disorders in women. Despite these remarkable epidemiologic data, limited clinical investigations have been conducted in this population. Recent changes in National Institutes of Health (NIH) and Food and Drug Administration (FDA) guidelines for clinical research have mandated the inclusion of women of reproductive age in future studies because pregnancy and childbirth represent naturally occurring life events accompanied by unparalleled neuroendocrine and psychosocial alterations. The interaction of these factors in the pathogenesis and treatment of both anxiety and affective disorders during the reproductive years comprises a virtually unexplored domain in psychiatric research today.

The potential adverse impact of untreated maternal depression during the formative years of a child's life remains largely unknown, further accentuating the need to include pregnant and postpartum women in research studies. Laboratory studies in rodents and primates have repeatedly demonstrated persistent adverse neuroendocrine and socialization phenomena associated with both prenatal and neonatal maternal stress.[2–4] Clinical data support the view that there is an adverse impact on mother-infant attachment and infant temperament associated with maternal depression[5,6] and that children of depressed mothers are more likely to suffer from adjustment disorders and childhood depression than children of nondepressed mothers.[7–9] The vulnerability of women to depression during the childbearing years and the data indicating adverse impact of maternal depression underscore the need for early identification, treatment guidelines, and further investigation about the etiopathogenesis of these disorders. This paper will provide an overview of the incidence of and the risk factors and treatment data associated with major depression during pregnancy and the postpartum period.

PREGNANCY

Since clinical lore has long posited that pregnancy is a time of emotional well-being, few data are available to support the position that pregnancy confers any protection against mental illness, although retrospective data support a decreased incidence of suicide during pregnancy.[10] Pregnancy also may be associated with a decrease in the frequency of panic attacks, though there is not universal agreement on the latter issue.[11,12] In contrast, a significant percentage of women with obsessive-

From the Department of Psychiatry and Behavioral Sciences (all authors) and the Department of Gynecology and Obstetrics (Dr. Stowe), Emory University School of Medicine, Atlanta, Ga.

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Reprint requests to: Zachary N. Stowe, M.D., Emory University Pregnancy and Postpartum Mood Disorders Program, PO Drawer A-F, Atlanta, GA 30322.

compulsive disorder (OCD) have their first symptoms during pregnancy.[13] Similar rates of major depression have been reported in gravid and nongravid women,[14] identified using self-report depression rating scales, such as the Beck Depression Inventory. Up to 70% of pregnant women expressed having depressive symptoms, with 10% to 16% of women fulfilling diagnostic criteria for a major depressive episode during pregnancy.[11,15–17] The overlap of symptoms between normal sequelae of pregnancy and those of major depression, e.g., fatigue, and the use of nonvalidated rating scales in this population render an accurate determination of prevalence difficult.

There appears to be both a professional and societal propensity to dismiss depressive symptoms such as changes in appetite, body weight, sleep, libido, and energy as related solely to the condition of pregnancy.[1,17] Further confounding the assessment of major depression during pregnancy is the failure to assess for medical disorders (including anemia, gestational diabetes, and thyroid dysfunction[18]) that could potentially contribute to depressive symptoms. For example, it was found that postpartum autoimmune thyroiditis actually begins during mid- to late pregnancy.[19,20] The contribution of thyroid gland dysfunction has undergone extensive investigation in nonpuerperal primary depression and, to some extent, in postpartum depression. An adverse impact of autoimmune thyroiditis during pregnancy on later infant cognition has been reported.[21] These issues also may provide confounds in infant follow-up studies of illness, development, and treatment exposure. Future prospective investigations should control for these variables to provide an accurate assessment of depression during pregnancy, as well as to lower the threshold for clinicians to rule out such illnesses when evaluating pregnant women. As with all disorders, treatment of major depression begins with early identification.

Several risk factors for depression during pregnancy have been identified, including a history of depression, a family history of depression, marital discord, recent adverse life events, and unwanted pregnancy.[22–25] Treatment of major depression during pregnancy remains largely empirical, with few definitive data, and, remarkably, no controlled studies to guide the clinician. Management of depression during pregnancy includes nonpharmacologic and somatic therapies, e.g., pharmacologic and electroconvulsive therapy (ECT). Although no decision is risk free, careful assessment of the risks and benefits for both mother and fetus is essential. The risks of untreated depression may include poor nutrition, disrupted sleep patterns, difficulty following medical and prenatal care recommendations, suicide, worsening of comorbid medical illness, and increased exposure to tobacco, alcohol, or drugs. Our clinical experience has demonstrated that pregnant women with depression may be exposed to medicines for symptom relief, i.e., diphenhydramine or hydroxyzine, rather than for depression (A.M.L., Z.N.S., C.B.N., unpublished observations, 1995).

There are no controlled treatment studies of depression during pregnancy, although data on the efficacy of interpersonal psychotherapy in pregnancy have been presented[26] and the use of psychotropic medications during pregnancy has been extensively reviewed.[12,27–29] A recent meta-analysis failed to find any evidence for teratogenicity for antidepressants during pregnancy.[30] First trimester exposure of 128 women to fluoxetine in a mean daily dose of 25.8 mg was not associated with any major or minor fetal malformations. The bulk of data have been derived from postmarketing surveillance. The Eli Lilly Company registry for fluoxetine is clearly the largest outcome study of antidepressant exposure with over 1400 cases.[31] Chambers et al.[32] studied 228 pregnant women taking fluoxetine and 264 pregnant women not taking fluoxetine. They concluded that women taking fluoxetine do not stand a greater chance of spontaneous pregnancy loss or major fetal anomalies, but women who take fluoxetine in their third trimester are at increased risk for perinatal complications. However, the study conclusions are limited by confounds of maternal age, tobacco use, and unblinded evaluations. Similar to the uncontrolled antidepressant data, 300 cases of ECT during pregnancy have been reviewed, and it appears that with proper preparation, ECT is a relatively safe and effective treatment for major depression in pregnant women.[29,33,34]

The long-term impact, if any, of somatic therapies during pregnancy on infant development remains unknown. The outcome of male rats exposed to fluoxetine in utero has been assessed. 5-HT neurons were assessed, and findings indicate age-dependent, region-specific, limited changes.[35] A decreased 5-HT content in the frontal cortex in prepubescent rats and a decreased midbrain 5-HT content in adult rats were observed. The implications of these findings for human exposure has yet to be determined. A detailed follow-up study by Nulman et al.[36] found that in utero exposure to tricyclic antidepressants (N = 80) or to fluoxetine (N = 55) does not affect global IQ, language development, or behavioral development in preschool children. Also obscure is the impact of untreated major depression during pregnancy on obstetrical outcome and infant development. The timing of mother-fetus bonding remains largely unexplored. Does bonding begin prior to delivery, and if so, is this impaired by depression during pregnancy? The clinician must weigh all of these factors and the parental concerns for the essentially unknown effects of pharmacologically treating or not treating the depression. Important in the evaluation of pregnant women is a careful risk-benefit assessment. We suggest that prior to initiation of treatment, except in emergent conditions, a medical workup of potential contributing disorders and a complete documentation of all medication and drug exposures be obtained. Whatever decision is realized by the clinician, pa-

tient, and significant other, the informed nature of the decision-making process should be documented in the patient's chart.

MISCARRIAGE AND PREGNANCY LOSS

Eighty-five percent of known pregnancies will result in a live birth. Thirty-six percent of women who have a miscarriage or stillbirth will experience severe depressive symptoms,[37] three times the rate of depressive symptoms in women who give birth to live babies.[38] Complaints such as depressed mood, anxiety, obsessive-compulsive behavior, and somatization increase in frequency in the 6-month period following a pregnancy loss.[39] Clarke and Williams[40] in 1979 found that 2 days after a miscarriage, women had moderate to high Beck Depression Inventory scores, or a rate 17% higher than the rate in women who had live births. Women who experience a miscarriage or intrauterine fetal demise demonstrate more emotional complaints at 2.5- and 6-month follow-up compared with women with live births, but not at 12- and 18-month follow-up.[39] Evidence indicates that the length of gestation before pregnancy loss is proportional to the severity of depressive symptoms.[39] The role of the neuroendocrine changes associated with pregnancy and how they may impact the depressive symptoms following pregnancy loss remain unclear. Complicating the potential contribution of neuroendocrine alterations is the overlap between depressive symptoms and bereavement. It is important not to discount these symptoms and deny treatment based on the professional projection that pregnancy loss may be distressful. Treatment for depression after miscarriage should be determined on an individual basis. The severity of the depression and method of treatment intervention warrant careful clinical assessment, as many of these women may be contemplating further pregnancies. Subsequent pregnancies in these women should be monitored due to the increased incidence of depression and anxiety in women with previous depression associated with reproductive loss.[39]

DEPRESSION ASSOCIATED WITH INFERTILITY

Interest is growing in the possible relationship between depression and infertility. One group found that women who were unable to conceive after 12 months of unprotected intercourse were twice as likely to report a history of depressive symptoms prior to attempting to conceive as women who were successful in conceiving within a 12-month period.[41] Additionally, women with high trait anxiety levels have a decreased rate of conception.[42] Careful consideration should be given to psychopharmacologic treatment of women trying to conceive. If women are treated with medication for depression, a plan of action must be charted for when conception occurs, as premature discontinuation of antidepressants may increase the rate of relapse of a major depressive episode. The relationship of depression and infertility clearly requires further scrutiny.

POSTPARTUM EVENTS

The event of childbirth is undeniably a time of copious biological, psychosocial, and economic alterations. A study by Kendall and colleagues[43] illustrated a marked increase in both general and psychotic psychiatric hospitalizations for postpartum women. A second study demonstrated that up to 12.5% of all psychiatric hospital admissions of women occur during the postpartum period.[44] Despite historical acknowledgment of this apparent time of increased vulnerability, official recognition of postpartum-onset mental illness has occurred only recently. DSM-IV now includes a modifier for "postpartum onset" of mood disorders with symptoms starting within 4 weeks postpartum.[45] The three major subtypes of postpartum mood disorders generally recognized are maternity blues, postpartum psychosis, and postpartum depression.[14] The number of case reports of postpartum onset of OCD and panic disorder is also increasing.[43] Postpartum mood disorders affect a significant number of new mothers and represent one of the most common obstetrical complications.

Maternity blues is a relatively mild emotional disturbance characterized by mood lability, depression, increased sensitivity to criticism, and despondency in the first 2 weeks postpartum. This condition affects 50% to 85% of postpartum women.[47–50] Symptoms of this condition are transient and require little intervention; however, approximately 20% of women with maternity blues will go on to develop major depression in the first postpartum year.[50,51] Postpartum psychosis is a rare condition occurring in one or two mothers in every 1000 live births, typically with onset in the first 6 weeks postpartum.[1,52,53] This is a severe psychiatric disorder, usually with acute onset of overt psychotic symptoms. A majority of these psychoses are bipolar disorder or unipolar depression disorder with psychotic features.[52] The third category of postpartum mood disorder, postpartum depression, affects 10% or more of adult women during the first postpartum year.

Postpartum Depression

Postpartum depression affects between 10% to 22% of women and up to 26% of adolescent mothers.[44,54–57] Symptoms typically appear within the first 6 weeks postpartum. For 60% of women, this will represent their first episode of depression.[58]

The overlap of depressive symptoms with those of the normal sequelae after childbirth can confound and complicate clinical identification. Changes in sleep, appetite, libido, fatigue, and worry are characteristic of both postpar-

tum depression and the normal postpartum period. Several risk factors have been identified for postpartum depression.[57] A personal or familial history of depression, especially of postpartum depression, creates a higher than average risk of experiencing a postpartum depressive episode.[54,59] Women with a previous episode of postpartum depression are at a 50% risk of recurrent episodes following subsequent pregnancies. Up to 30% of women who have a history of depression prior to conception will develop postpartum depression.[22] Anxiety and depression during pregnancy have been reported to be indicators for future postpartum depression.[22,60] Additional risk factors that have been identified include poor postpartum support, stressful or adverse life events, marital instability, infants with health problems or disagreeable temperaments, and unwanted pregnancies.[22,51,61–65] In contrast to the clearly established risk factors, the etiology of postpartum depression remains an enigma.

Hormonal theories have been postulated as triggers for postpartum emotional vulnerability.[66,67] To date, studies of various neurotransmitter systems and other neuroregulators have not provided evidence that any one distinguishes women with postpartum depression from women without postpartum depression.[68–70] Postpartum women with depressive symptoms and major depression have increased urinary excretion of cortisol[50]; however, any measure of hypothalamic-pituitary-adrenal axis activity is difficult to interpret because of alterations related to pregnancy and childbirth.[70] Platelet-binding studies demonstrated an increase in the dissociation constant, K_d, for platelet [^{3}H]-imipramine binding on postpartum Day 5, which correlated with depression at 6 weeks postpartum.[71] In contrast, our group did not find a difference in the number of platelet [^{3}H]-paroxetine-binding sites nor in the K_d.[72] Both [^{3}H]-imipramine and [^{3}H]-paroxetine are the serotonin transporter sites where serotonin selective reuptake inhibitors are believed to produce their therapeutic action.

Depression has been known to occur in patients with thyroid disease of various sorts. The changes associated with gestation and parturition involving the hypothalamic-pituitary-thyroid (HPT) axis make it suspect as a possible causal or contributing agent in postpartum mental distress. Serum total thyroxine and triiodothyronine concentrations are elevated during pregnancy secondary to increases in thyroxine-binding globulin (TBG), estrogen stimulation of hepatic synthesis of TBG, and a decrease in TBG breakdown.[73,74] A follow-up study of women who exhibited positive antithyroid antibodies at 16 weeks of gestation showed that they had a 50% likelihood of developing postpartum thyroid dysfunction.[75] The exact role of the HPT axis in the pathophysiology of postpartum depression remains obscure. Considering the evidence demonstrating HPT axis dysfunction in nonpuerperal affective disorders, the gender predominance of HPT axis dysfunction, and the possible belated HPT axis recovery in the postpartum period, clinical evaluation of thyroid function in women with suspected postpartum mood disorders is warranted.

The neuroendocrine/neurotransmitter studies provide no definitive measure for use as a diagnostic adjunct; however, several studies have developed rating scales to aid in early identification of maternity blues and postpartum depression. Emotional complaints that exist after the first 2 weeks postpartum or complaints separated by more than 3 days should serve as an impetus for the clinician to inquire further about depressive symptoms. A complete psychiatric history and survey of the current psychosocial situation are essential in assessing such patients. Problematic is the overlap of symptomatology between depression and normal postpartum progression in this population, which may lead to misidentification (false positives) or failure to identify depression in postpartum women (false negatives). There exist measures specifically developed for this population. One physician-administered screening procedure is the Postpartum Depression Checklist (PDC). The PDC can be used to identify women who need further evaluation for depressive symptoms.[15] The Edinburgh Postnatal Depression Scale, which has evolved into a multilingual, self-rated measure, correlates well with physician-rated scales and a depressive disorder diagnosis.[76] It is important to remember that no single measure can substitute for a clinical interview that gives consideration to the postpartum condition.

After women have been identified as suffering from postpartum depression, all treatment options should be reviewed, though few treatment studies for postpartum depression have been conducted. O'Hara and colleagues utilized interpersonal psychotherapy in a group of 12 women with postpartum depression and demonstrated a positive response in 9 of the women 12 weeks after beginning therapy.[77,78] Psychosocial interventions have been shown to be effective in improving symptoms and disruptive interpersonal issues for postpartum women.[78,79] Estrogen has been found to be an effective treatment for postnatal depression. Transdermal 17 β-estradiol 200 μg/day was given to 34 women for 3 months. Cyclical dydrogesterone was then administered, 10 mg/day for 12 days of each month for an extra 3 months. Endometrial curettage at the end of treatment showed endometrial change in 3 women. Additional research is needed to determine the effective minimum dose and treatment time.[80–82] Our group has reported the highly efficacious treatment response to sertraline monotherapy for women with postpartum depression.[83] Wisner and Perel reported successful treatment with nortriptyline in postpartum women.[84] National and international support groups (Depression After Delivery, Postpartum Support International) have been established to assist women and their families by providing education, support, and professional referrals.

Breastfeeding is an important consideration in treating women with postpartum depression. The majority of pro-

fessional organizations support breastfeeding as the ideal form of nutrition for infants. It is important to respect a woman's desire to breast-feed. Social pressures and guilt resulting from cessation of breastfeeding can become additional and potentially preventable stressors for postpartum women. All antidepressants studied have been found to be excreted in breast milk, and deleterious effects have not been reported. Long-term studies evaluating neurobehavioral effects and teratogenicity are not available. One study measured serum concentrations of nortriptyline in seven nursing mothers and their infants. The study did not detect nortriptyline in the infants' sera, although two of the four infant sera samples contained low concentrations of the metabolite 10-hydroxynortriptyline; no evidence of adverse effects to the infants was reported.[84] Our group compared the infants of women treated with sertraline monotherapy who breast-fed with those of sertraline-treated women who bottle-fed and failed to find any adverse impact of these medication periods in mother on infant growth, immunologic benefits, or developmental milestones achieved, despite the fact that sertraline and its metabolite, desmethylsertraline, are excreted in human breast milk.[85] Another group tested sertraline and norsertraline levels in plasma of mothers and breastfed infants. All infant plasma levels were < 2 ng/mL for either sertraline and norsertraline or norsertraline alone and have demonstrated no adverse effects of exposure on short-term follow-up.[86] It has been proposed that timing feedings or collections of breast milk based on when serum concentrations in the breast milk are low may be beneficial.[87] Further study is needed to determine how to psychopharmacologically treat this group of women. ECT has been used on this population with beneficial outcomes in treating depression. This method of treatment can be used on breastfeeding mothers without risk to the nursing infant.[29]

Prophylaxis and prevention are applicable for some potential postpartum depression candidates. Patients who are at risk for postpartum depression should be educated about postpartum mood disorders. Prophylaxis may be appropriate for women with a history of postpartum depression or nonpuerperal major depression. Women at high risk for postpartum depression may benefit from counseling, enhanced social support, and education prior to childbirth.[88] Wisner and Wheeler[89] compared the rates of recurrent postpartum depression between a group of 17 women who elected prophylactic antidepressant treatment following childbirth and a control group of postpartum women who opted for observation rather than pharmacologic intervention. All subjects had experienced a previous episode of postpartum depression and were monitored throughout the postpartum period. Prophylaxis with tricyclic antidepressants reduced the recurrence of postpartum depression to 6.7% compared with a 62.5% relapse rate in the control group.[89]

Table 1. General Recommendations for Choosing a Medication for Patients Who Are Pregnant or Breastfeeding

Medication appropriate for the diagnosis
Patient history of positive response to a medication
Prior use of a medication in a special population
Dosing flexibility
Safety in overdose

Long-term treatment studies in women with postpartum depression are not yet available. Proper education and identification of women who have significant risk factors for postpartum depression are the cornerstone to prevention and early intervention.

CONCLUSION

There is no evidence that pregnancy confers any protection against depressive disorders; indeed, evidence indicates that the postpartum period is one of increased vulnerability for onset of major depressive episodes. No definitive treatment guidelines exist to guide clinicians. Should medication be appropriate, Table 1 provides some recommendations for selecting a medication during pregnancy or lactation. The unknown risks of untreated mental illness on the health and development of mothers and infants render it essential that long-term research on biological, psychosocial, and treatment strategies for the affected population is conducted. Treatment in this population requires consideration of multiple issues and a careful risk-benefit assessment. The potential deleterious effects of major depression during pregnancy and the puerperium to a woman's well-being and her infant's development should be included in the assessment. We are confident that our recommendations provide a foundation for clinicians to identify, educate, and treat women affected or identified as at risk for postpartum mood disorders.

Drug names: diphenhydramine (Benadryl and others), fluoxetine (Prozac), hydroxyzine (Atarax and others), imipramine (Tofranil and others), nortriptyline (Pamelor and others), paroxetine (Paxil), sertraline (Zoloft).

REFERENCES

1. Weissman MM, Olfson M. Depression in women: implications for health care research. Science 1995;269:799–801
2. Plotsky PM, Meaney MJ. Early, postnatal experience alters hypothalamic corticotropin-releasing factor (CRF) mRNA, median eminence CRF content and stress-induced release in adult rats. Molecular Brain Research 1993;18:195–200
3. Coplan JD, Andrews MW, Rosenblum LA, et al. Persistent elevations of cerebrospinal fluid concentrations of corticotropin-releasing factor in adult non-human primates exposed to early life stressors: implications for the pathophysiology of mood and anxiety disorders. Proc Natl Acad Sci U S A 1996;93:1619–1623
4. Ladd CO, Owens MJ, Nemeroff CB. Persistent changes in corticotropin-releasing factor neuronal systems induced by maternal deprivation. Endocrinology 1996;137:1212–1218
5. Campbell SB, Cohn JF, Meyers T. Depression in first-time mothers: mother-infant interaction and depression chronicity. Dev Psychol 1995;31:349–357

6. Teti DM, Messinger DS, Gelfand DM, et al. Maternal depression and the quality of early attachment: an examination of infants, preschoolers, and their mothers. Dev Psychol 1995;31:364–376
7. Cutrona CE, Troutman BR. Social support, infant temperament and parenting self-efficacy: a mediational model of postpartum depression. Child Dev 1986;57:1507–1518
8. Hopkins J, Campbell SB, Marcus M. Role of infant-related stressors in postpartum depression. J Abnorm Psychol 1987;96:237–241
9. Gelfand DM, Teti DM. How does maternal depression affect children? Harvard Mental Health Letter November, 1995
10. Appleby L. Suicide during pregnancy and in the first postnatal year. BMJ 1991;302:137–140
11. Klein MH, Essex MJ. Pregnant or depressed? the effect of overlap between symptoms of depression and somatic complaints of pregnancy on rates of major depression in the second trimester. Depression 1995;2:308–314
12. Cohen LS, Heller VL, Rosenbaum JF. Treatment guidelines for psychotropic drug use in pregnancy. Psychosomatics 1989;30:25–33
13. Neziroglu F, Anemone R, Yaryura TJA. Onset of obsessive compulsive disorder in pregnancy. Am J Psychiatry 1992;149:947–950
14. O'Hara MW. Postpartum mental disorders. In: Droegemeuller W, Sciarra J, eds. Gynecology and Obstetrics. Philadelphia, Pa: Lippincott; 1991
15. Beck CT. Screening methods for postpartum depression. J Obstet Gynecol Neonatal Nurs 1995;24:308–312
16. Affonso DD, Lovett S, Paul SM, et al. A standardized interview that differentiates pregnancy and postpartum symptoms from perinatal clinical depression. Birth 1990;17:121–130
17. Kumar R, Robson KM. A prospective study of emotional disorders in childbearing women. Br J Psychiatry 1984;144:35–47
18. Pedersen CA, Stern RA, Pate J, et al. Thyroid and adrenal measures during late pregnancy and the puerperium in women who have been major depressed or who become dysphoric postpartum. J Affect Disord 1993;29: 201–211
19. Harris B, Lovett L, Roberts S, et al. Cardiff puerperal mood and hormone study. Horm Res 1993;39:138–145
20. Harris B. A hormonal component to postnatal depression. Br J Psychiatry 1993;163:403–405
21. Jansson R, Bernander S, Karlsson A, et al. Autoimmune thyroid dysfunction in the postpartum period. J Clin Endocrinol Metab 1984;58:681–687
22. O'Hara MW. Social support, life events and depression during pregnancy and the puerperium. Arch Gen Psychiatry 1986;43:569–573
23. Kitamura T, Shima S, Sugawara M, et al. Psychological and social correlates of the onset of affective disorders among pregnant women. Psychol Med 1993;23:967–975
24. Gotlib LA, Whiffen VE, Mount JH, et al. Prevalence rates and demographic characteristics associated with depression in pregnancy and postpartum. J Consult Clin Psychol 1989;57:269–274
25. Frank G, Kupfer D, Jacob M, et al. Pregnancy-related affective disorders among women with recurrent depression. Am J Psychiatry 1987;144: 288–293
26. Spinelli M. Interpersonal therapy in antepartum depression. Presented at the 149th annual meeting of the American Psychiatric Association; May 8, 1996; New York, NY
27. Miller LJ. Psychiatric medication during pregnancy: understanding and minimizing the risks. Psychiatr Ann 1994;24:69–75
28. Stowe ZN, Nemeroff CB. Psychopharmacology during pregnancy and lactation. In: Schatzberg AF, Nemeroff CB, eds. Textbook of Psychopharmacology. Washington, DC: American Psychiatric Press; 1995:823–837
29. Wisner KL, Perel JM. Psychopharmacologic agents and electroconvulsive therapy during pregnancy and the puerperium. In: Cohen RL, ed. Psychiatric Consultation in Childbirth Settings: Parent- and Child-Oriented Approaches. New York, NY: Plenum Medical Book Company; 1988:165–206
30. Altshuler LL, Cohen L, Szuba MP, et al. Pharmacologic management of psychiatric illness in pregnancy: dilemmas and guidelines. Am J Psychiatry 1996;153:592–606
31. Pastuszack A, Schick-Boschetto B, Zuber C, et al. Pregnancy outcome following first-trimester exposure to fluoxetine (Prozac). JAMA 1993;269: 2246–2248
32. Chambers CD, Johnson KA, Dick LM, et al. Birth outcomes in pregnant women taking fluoxetine. N Engl J Med 1996;335:1010–1015
33. Miller LJ. Use of electroconvulsive therapy during pregnancy. Hosp Community Psychiatry 1994;45:444–450
34. Walker R, Swartz CM. Electroconvulsive therapy during high-risk pregnancy. Gen Hosp Psychiatry 1994;16:948–953
35. Cabreera-Vera TM, Garcia F, Pinto W, et al. Effect of prenatal paroxetine (Prozac) exposure on brain serotonin neurons in prepubescent and adult male rat offspring. J Pharmacol Exp Ther 1997;280:138–145
36. Nulman I, Rovet J, Stewart DE, et al. Neurodevelopment of children exposed in utero to antidepressant drugs. N Engl J Med 1997;336:258–262
37. Neugebauer R, Kline J, O'Connor P, et al. Depressive symptoms in women in the six months after miscarriage. Am J Obstet Gynecol 1992;166: 104–109
38. Neugebauer R, Kline J, O'Connor P, et al. Determinants of depressive symptoms in the early weeks after miscarriage. Am J Public Health 1992; 82:1332–1339
39. Janssen JJEM, Cuisinier MCJ, Hoogduin KAL, et al. Controlled prospective study on the mental health of women following pregnancy loss. Am J Psychiatry 1996;153:226–230
40. Clarke M, Williams AJ. Depression in women after perinatal death. Lancet 1979;4:916–917
41. Lapane KL, Zierler S, Lasater TM, et al. Is a history of depressive symptoms associated with an increase in infertility in women? Psychosom Med 1995;57:509–513
42. Demyttenaere K, Nijs P, Evers-Kiebooms G, et al. Personality characteristics, psychoendocrinological stress and outcome of IVF depend upon the etiology of infertility. Gynecol Endocrinol 1994;8:233–240
43. Kendall RE, Chalmers JC, Platz C. Epidemiology of puerperal psychosis. Br J Psychiatry 1987;150:662–673
44. Duffy CL. Postpartum depression: identifying women at risk. Genesis 1983; June/July:11,21
45. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
46. Sichel DA, Cohen LS, Rosenbaum JF, et al. Postpartum onset of obsessive-compulsive disorder. Psychosomatics 1993;34:277–279
47. Levy V. The maternity blues in post-partum and post-operative women. Br J Psychiatry 1987;151:368–372
48. Hapgood CC, Elkind GS, Wright JJ. Maternity blues: phenomena and relationship to later postpartum depression. Aust N Z J Psychiatry 1988;22: 299–306
49. Kennerley H, Gath D. Maternity blues: detection and measurement by questionnaire. Br J Psychiatry 1989;155:356–362
50. O'Hara MW, Schlechte JA, Lewis DA, et al. Prospective study of postpartum blues: biologic and psychosocial factors. Arch Gen Psychiatry 1991; 48:801–806
51. Campbell SB, Cohn JF, Flanagan C, et al. Course and correlates of postpartum depression during the transition to parenthood. Development and Psychopathology 1992;4:29–47
52. McGorry P, Conell S. The nosology and prognosis of puerperal psychosis: a review. Compr Psychiatry 1990;31:519–534
53. Sibert TE. Recognizing and Treating Postpartum Depression. Report #11. Clinical News Reporter. Greenwich, England; 1993:11
54. Richards JP. Postnatal depression: a review of recent literature. Br J Gen Pract 1990;40:472–476
55. Cooper PJ, Murray L. Course and recurrence of postnatal depression: evidence for the specificity of the diagnostic concept. Br J Psychiatry 1995; 166:191–195
56. Troutman B, Cutrona C. Nonpsychotic postpartum depression among adolescent mothers. J Abnorm Psychol 1990;99:69
57. Stowe ZN, Nemeroff CB. Women at risk for postpartum-onset major depression. Am J Obstet Gynecol 1995;173:639–645
58. Stowe ZN, Landry JC, Porter MR. The use of depression rating scales in women with postpartum depression. In: New Research Program and Abstracts of the 148th Annual Meeting of the American Psychiatric Association; May 23, 1995; Miami, Fla. Abstract NR309:138
59. Playfair HR, Gowers JI. Depression following childbirth—a search for predictive signs. J R Coll Gen Pract 1981;31:201–208
60. O'Hara MW, Rehm LP, Campbell SB. Predicting depressive symptomatology: cognitive-behavioural models and postpartum depression. J Abnorm Psychol 1982;91:457–461
61. Watson JP, Elliott SA, Rugg AJ, et al. Psychiatric disorder in pregnancy and the first postnatal year. Br J Psychiatry 1984;144:453–462
62. Martin CJ, Brown GW, Goldberg DP, et al. Psychosocial stress and puerperal depression. J Affect Disord 1989;16:283–293
63. Stein A, Cooper PJ, Campbell EA, et al. Social adversity and perinatal complications: their relation to postnatal depression. BMJ 1989;298: 1073–1074

64. Wolman W, Chalmers B, Hofmeyr GJ, et al. Postpartum depression and companionship in the clinical birth environment: a randomized, controlled study. Am J Obstet Gynecol 1993;168:1388–1393
65. Knight RG, Thirkettle JA. The relationship between expectations of pregnancy and birth, and transient depression in the immediate post-partum period. J Psychosom Res 1987;31:351–357
66. Sichel D, Cohen L. Oestrogen and the prevention of severe postnatal mental illness. Neuropsychopharmacology 1994;10:904S
67. Alder EM, Cox JL. Breastfeeding and post-natal depression. J Psychosom Res 1983;27:139–144
68. Harris B, John S, Fung H, et al. The hormonal environment of post natal depression. Br J Psychiatry 1989;154:660–667
69. Nomura J. Cross cultural and neuroendocrine aspects of postpartum psychiatric illness. Neuropsychopharmacology 1994;10:902S
70. Smith R, Cubis J, Binsmead M, et al. Mood changes, obstetric experience and alterations in plasma cortisol beta-endorphin and corticotrophin releasing hormone during pregnancy and the puerperium. J Psychosom Res 1990;34:53–69
71. Hannah P, Adams D, Glover V, et al. Abnormal platelet 5-hydroxytryptamine uptake and imipramine binding in postnatal dysphoria. J Psychiatr Res 1992;26:69–75
72. Stowe ZN, Owens MJ, Nemeroff CB. Pilot study of platelet serotonin transporter binding sites in women with postpartum depression. In: New Research Program and Abstracts of the 147th Annual Meeting of the American Psychiatric Association; May 25, 1994; Philadelphia, Pa. Abstract NR422:166
73. Glinoer D, DeNayer P, Bourdoux P, et al. Regulation of maternal thyroid function during pregnancy. J Clin Endocrinol Metab 1990;71:276–287
74. Ain KB, Mori Y, Refetoff S. Reduced clearance rate of thyroxine-binding globulin (TBG) with increased sialylation: a mechanism for estrogen-induced elevation of serum concentration. J Clin Endocrinol Metab 1987;65:686–696
75. Harris B, Othman S, Davies JA, et al. Association between postpartum thyroid dysfunction and thyroid antibodies and depression. BMJ 1992;305: 152–156
76. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Br J Psychiatry 1987;150:782–786
77. Stuart S, O'Hara MW. Interpersonal psychotherapy for postpartum depression: a treatment program. Journal of Psychotherapy Practice and Research 1995;4:18–29
78. O'Hara MW. Psychosocial therapies in the peripartum period. Presented at the 147th annual meeting of the American Psychiatric Association; May 21–26, 1994; Philadelphia, Pa
79. Stuart S, O'Hara MW. Interpersonal Psychotherapy for Postpartum Depression: A Treatment Manual. Iowa City, Iowa: University of Iowa; 1993: 1–11
80. Gregorie AJ, Kumar S, Everitt B, et al. Transdermal oestrogen for treatment of severe postnatal depression. Lancet 1996;347:930–933
81. Gregoire AJP, Henderson A, Kumar R, et al. A controlled trial of oestradiol therapy for postnatal depression. Neuropsychopharmacology 1994;10: 901S
82. Murray D. Oestrogen and postnatal depression. Lancet 1996;347:918–919
83. Stowe ZN, Casarella J, Landry J, et al. Sertraline in the treatment of women with postpartum major depression. Depression 1995;3:49–55
84. Wisner KL, Perel JM. Serum nortriptyline levels in nursing mothers and their infants. Am J Psychiatry 1991;149:1234–1236
85. Winn S, Stowe ZN, Landry JC, et al. Sertraline in breast milk and nursing infants. In: New Research Program and Abstracts of the 148th Annual Meeting of the American Psychiatric Association; May 22, 1995; Miami, Fla. Abstract NR72:73
86. Mammen OK, Perel JM, Rudolph G, et al. Sertraline and norsertraline levels in three breastfed infants. J Clin Psychiatry 1997;58:100–103
87. Altshuler LL, Burt VK, McMullen M, et al. Breastfeeding and sertraline: a 24-hour analysis. J Clin Psychiatry 1995;56:243–245
88. Gordon RE, Gordon KK. Social factors in prevention of postpartum emotional problems. Obstet Gynecol 1960;15:433–438
89. Wisner KL, Wheeler SB. Prevention of recurrent postpartum onset major depression. Hosp Community Psychiatry 1994;45:1191–1196