The Treatment of Postpartum Depression: Minimizing Infant Exposures

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The first 3 postpartum months represent a high-risk period for psychiatric illnesses. This article reviews the prevalence and diagnostic criteria for postpartum illnesses, including the "maternal blues," postpartum depression, and postpartum psychosis. Pharmacologic treatment of these disorders is often complicated by a patient's desire to breast-feed, yet there are no controlled trials of antidepressant treatment during lactation. Infant exposure and limitations to monitoring infant sera are reviewed. Lastly, a model and guide for reducing fetal and infant exposures is presented.

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The earliest extant documentation of postpartum mental illness was provided by Hippocrates in 400 B.C. and Tortula in the 1st century of the Common Era. Despite its recognition in antiquity and an extensive line of inquiry into its pathogenesis that dates back to the mid-19th century, postpartum depression remains an enigmatic syndrome. Many clinicians and patients accept the notion that biological aberrations precipitate the onset of postpartum psychiatric illness; however, research to date has failed to consistently identify any biological substrate associated with postpartum mental illness. While the factors driving postpartum mental illness remain obscure, recent legislative reforms in New Jersey to develop an awareness campaign, postpartum support groups, and news media have served to underscore the heightened vulnerability to the development of mood disorders during the postpartum period.

In fact, a disproportionate share of psychiatric hospital admissions for women occur during the first postpartum year.[1,2] It remains unclear whether postnatal psychiatric illness is a consequence of a set of syndromes unique to the postpartum or whether the postpartum period serves as a crucible for exacerbating preexisting illness. The postnatal increase in psychiatric admissions may also result from the presentation of women with limited adaptive reserve that were subclinical prior to childbirth. Etiologic concerns fail in the shadow of the burgeoning evidence that postnatal maternal mental illness poses a risk to the mother-infant dyad. Over 4 decades of clinical and laboratory animal research have repeatedly demonstrated that maternal mental illness, maternal separation, and maternal stress have an enduring negative impact upon offspring.

Recognizing the common prevalence and potential adverse impact of postpartum depression upon child development, early identification and effective treatment models are clearly needed. The need for treatment and the potential impact of the illness are often complicated by a mother's desire to breast-feed. Taken together, the increasing proportion of women planning to breast-feed, the support for breastfeeding by the majority of professional groups, and the continuing data that demonstrate the benefits of extended breastfeeding (> 12 months) for both mother and infant present a unique, potentially guilt-laden decision for new mothers. Understandably, many new mothers are reluctant to use psychotropic medication during lactation.[3] This decision is complicated by the lack of consensus with respect to infant monitoring and an international disparity with respect to defining the infant's exposure. We offer a more detailed extension of the model for reducing fetal and infant exposures, as a guide to clinical decision making during the postpartum.[4,5] This exposure reduction model is based on the premise that the treatment of new mothers does not occur in a psychosocial vacuum. This model recognizes that there are various levels of exposure both known and suspected (or unconfirmed), which are imposed by both the treatment options and by the illness itself.

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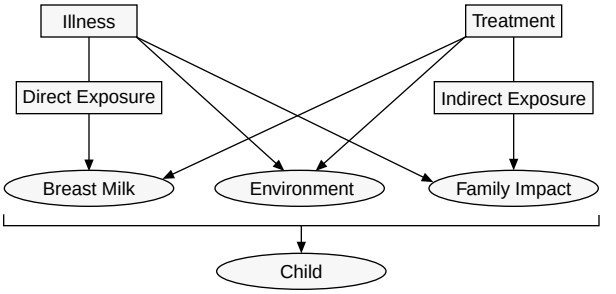
DEFINING EXPOSURE

The primary problem of exposure in psychiatry is the lack of a clear definition. In the context of postpartum mental illness, there are 3 dimensions to the question: Who is exposed? How are they exposed? To what are they exposed? Obviously, the "who" of exposure includes the new mother, but postnatal emotional impairment and its treatment must include exposure for the neonate as well. If the maternal impairment is severe or exhausts maternal emotional reserves, exposure extends to other members of the family, friends, and coworkers. The aspects of "how" and "to what" are not as readily discernible.

First, we must consider how exposure occurs. Exposure may take place either directly or indirectly. *Direct exposure* is imparted by any substrate (e.g., neurobiological, pharmacologic, environmental toxins) that comes into direct contact with an individual. *Indirect exposure* is conveyed by the influence of a substrate upon the individual's environment. With respect to the patient, a new mother suffering from postpartum depression, this distinction is largely semantic. The mother's direct exposures include the illness itself and the treatment that she receives. Her indirect exposures include the consequences of the illness (e.g., fractured relationships, occupational impairment) and the investment that she must make in the treatment (e.g., cost of medication, time for therapy sessions).

The distinction between direct and indirect exposure is perhaps more relevant when considering the impact of postpartum depression and its treatment options upon the newborn child. As illustrated in Figure 1, the clinician must consider the baby's indirect exposure to maternal illness via impaired mother/infant attachment, impairment of maternal care, and the impact of the illness on the family environment and overall family stability. The breastfeeding infant is vulnerable to direct exposure via the impact of maternal illness on breast milk. For example, if a breastfeeding mother with depression is more likely to consume alcohol, smoke cigarettes, or take other medications (both prescription and over-the-counter agents) when she is depressed, these behaviors all constitute direct exposures to her infant via breast milk. The impact of the illness, if any, upon the constituents of breast milk represents a direct exposure of the infant to maternal illness. Similarly, all potential treatment options for postpartum depression pose some degree of exposure. These exposures could include the indirect impact of the side effects of maternal treatment impairing daily functioning (e.g., post–electroconvulsive therapy [ECT] confusion) or influencing the parental relationship (e.g., sexual dysfunction), a delay in treatment response extending the exposure to the illness, and separation if hospitalization is required. The breastfed infant has a variety of direct exposures to treatment modalities as well. All psychotropic medications studied are excreted into breast milk,[6,7] the anesthetic agents utilized in ECT are found in breast milk, and the impact of sleep deprivation and light therapy, if any, on the constituents of breast milk have not been delineated.

Figure 1. Postpartum Depression: Pathways of Exposure



The "what" of exposure may be defined both phenomenologically and biologically. Phenomenologically, major depression incorporates a constellation of emotional, cognitive, and neurovegetative symptoms that, by definition, impair function. When attempting to care for a newborn infant in the midst of recovering from the physical demands of pregnancy and delivery, the intrusion of neurovegetative symptoms is most unwelcome. For example, maternal sleep disturbance during the immediate postpartum, already common in the care of an infant but further exacerbated by depression, can elicit a vicious cycle that impedes the physical recovery from delivery while further exacerbating postpartum mood disturbance.

Biologically defined exposure, while far less studied, appears easier to quantify and is often under greater direct influence by the clinician. It is unclear whether women with postpartum depression demonstrate the same neuroendocrine alterations seen in nonpuerperal major depression. The presence of such alterations could potentially alter breast milk contents. When comparing treatment options, it must be recognized that every treatment modality affords some degree of exposure. When considering treatment exposure, our attention invariably focuses upon the use of psychotropic medications. However, the use of anesthetic agents in ECT and the impact of sleep deprivation or light therapy upon melatonin secretion indicate that some level of biological exposure is always present for the breastfed infant.

The DSM-IV modifier for postpartum onset notes the frequency of obsessional and anxiety symptoms. Confirmed by Wisner and colleagues,[8] the alterations in maternal care that arise when a new mother either evades the source of her anxiety or overcompensates for it likely represent an example of indirect exposure to the infant of maternal mental illness.

Consequently, the mother with depressive symptoms who wishes to breast-feed faces difficult questions: Do I take medication? Do I breast-feed my baby? Do I do both? Do I choose one or the other? Although it is beyond the

scope of this review to discuss the benefits of breastfeeding, most professional groups support breast milk as the ideal source of nutrition for infants.[9] Thus, any decision to discontinue breastfeeding in order to take a medication (when the mother otherwise wishes to breast-feed) represents an exposure to the infant. In this case, the indirect exposure associated with antidepressant treatment is the absence of breastfeeding and the loss of potential benefits.

In the following sections, the facets of such an exposure model are discussed in greater detail to establish the foundation for treatment planning under the aegis that the least number of exposures is the best treatment option. Finally, we will briefly discuss the future directions for research and clinical management of postpartum depression.

EXPOSURE TO ILLNESS

Phenomenology of Postpartum Illness

The perfect childbirth and motherhood experience as depicted in parenting magazines essentially is a myth. Women seldom complete pregnancy without taking any prescription medications, have uncomplicated labor, deliver without anesthetic agents, and have a cosmetically perfect child who breast-feeds without difficulty.[10] This ideal arguably constitutes less than 2% of all pregnancies. In fact, the first 3 postpartum months represent an extremely high-risk period for significant psychiatric illness. For many women, it is clearly not the period of well-being that is portrayed in the lay press and magazines.

The ongoing debate of the clinical characteristics and etiology of postpartum mental illness began in the mid-19th century. For example, in 1845 Esquirol described a variety of postnatal mood syndromes and contested their purported association with lactation.[11] Marce, in a case series of 44 women published in 1858, suggested that postpartum mental illnesses could be classified into 2 groups: those with early onset marked primarily by cognitive symptoms such as confusion or delirium, and those with late onset characterized by a predominance of physical symptoms.[12] By the turn of the century, the suggestion that postpartum mental illnesses were clinically distinct from mental disorders occurring at other times was disputed. Consequently, the American Psychiatric Association removed the term *postpartum* from the psychiatric nosology and constructed a diagnostic scheme that relied exclusively upon the presenting symptoms of the illness.[13] Postpartum mental illnesses were thereafter commonly termed *schizophrenic*, *affective*, or *toxic* (i.e., infection-related) disorders.[14] Although it is not reflected in the DSM-IV nosology, most researchers agree that there is a continuum of severity in postnatal mood disturbance that can be coarsely divided into 3 categories: postpartum blues, postpartum depression, and postpartum psychosis.

Postpartum blues. Postpartum blues (maternity blues, baby blues) is the most common postnatal mood disturbance, affecting from 50% to 80% of new mothers.[15,16] Symptoms of the postpartum blues include mild depression, irritability, confusion, mood instability, anxiety, headache, fatigue, and forgetfulness, which usually begin within the first 2 weeks after delivery and last from a few hours to a few days. Postpartum blues seldom warrants professional attention and as such is not considered a "disorder" in the strictest sense of the term.

Nonetheless, it is important to identify women with postpartum blues. Experiencing maternity blues increases the risk for ultimately developing a postpartum depression.[17] In fact, as many as 20% of women who experience postpartum blues succumb to a major depressive episode during the first postnatal year.[16,18] Thus, careful observation of symptom progression during late pregnancy and the early postpartum period is warranted. Women at risk for postpartum blues are more likely to have a personal or family history of depression, to experience premenstrual dysphoria, to have recent stressful life events or poor social adjustment, to be depressed or anxious during pregnancy, to exhibit a sense of pessimism during late pregnancy, to be especially fearful about labor, to feel ambivalent about the pregnancy, or to view the pregnancy as emotionally difficult.[13,19,20]

Postpartum depression. Postpartum depression (PPD), termed *major depressive disorder with postpartum onset* in DSM-IV, is a major depressive episode that begins within the first 4 weeks after delivery. Highly variable in severity and duration,[21] the prevalence of PPD ranges from 5% to over 20%[22] with the highest rates occurring in adolescent mothers.[23] The wide variation in prevalence rates belies the difficulty in reliably diagnosing PPD using current assessment methods and diagnostic criteria. For example, many of the supposedly "normal" sequalae of the postpartum, such as disturbances in sleep, energy, and weight, overlap with depressive symptoms. Furthermore, accurate diagnosis is often hampered by poor screening practices for potential medical causes (i.e., anemia, diabetes, hypothyroidism) that might contribute to depressive symptoms.[24] Depression rating scales specific to this patient population have been developed to aid clinicians in screening during the postpartum period, including the Edinburgh Postnatal Depression Rating Scale[25] and the Postpartum Depression Checklist.[26] However, prenatal screening of women at high risk for postpartum-onset depression is an emerging standard of care.

Although no specific demographic characteristics are associated with PPD, there are numerous risk factors for PPD that can be identified prior to delivery. These include a personal or family history of depression, a prior episode of PPD, depression or anxiety during pregnancy, an unplanned or unwanted pregnancy, recent stressful life events or poor social support, and marital discord.[22,27–30] In addition, the occurrence of maternity blues or neonatal infant medical problems increases the susceptibility to PPD.[19,27–29]

Postpartum psychosis. Postpartum psychosis (PPP), the most severe of the postpartum syndromes, is relatively rare, occurring in less than 2 of every 1000 deliveries.[2] The onset of PPP usually begins within the first 3 weeks after delivery and often within just a few days.[31] Although brief psychotic disorder and acute exacerbations of schizophrenia may occur during the postpartum period, over 70% of psychotic episodes during the postpartum represent a psychotic episode of bipolar disorder or major depression.[32] The symptoms of PPP include delusions, hallucinations, rapid mood swings ranging from depression and irritability to euphoria, sleep disturbances, and obsessive ruminations about the baby. Since approximately 5% of women with PPP commit suicide and 4% commit infanticide,[33] PPP is a psychiatric emergency that invariably warrants hospitalization.

The diagnosis of PPP also carries profound prognostic implications. Nearly two thirds of these women will experience a relapse after subsequent pregnancies.[34,35] In addition, approximately two thirds will suffer subsequent nonpuerperal psychotic episodes.[34–36]

Validity of DSM-IV criteria. Considerable debate has focused upon the validity of the psychiatric nosology regarding postpartum depression. Two key questions merit attention. First, is PPD a distinct syndrome or simply a postpartum occurrence of major depressive disorder? Second, is the 4-week window for postpartum onset, as defined in DSM-IV, accurate?

The first question, whether PPD is a distinct diagnosis, has drawn conflicting opinions. One early study described higher levels of anxiety and irritability but less prominent neurovegetative symptoms and suicidal ideation in PPD when compared with nonpuerperal depression.[37] Conversely, other studies that utilized standardized rating scales and structured interviews have not shown significant phenomenological differences.[38–40] This debate underlies the nosologic evolution of PPD and PPP in the DSM. For example, PPP is described in DSM-II as a "psychosis associated with childbirth" and is included among the organic psychoses. In DSM-III, PPP is considered an example of an atypical psychosis. Finally, DSM-IV includes "postpartum onset" as a diagnostic specifier of mood disorders and brief psychotic disorder when symptom onset occurs within 4 weeks after delivery. The current nosology, therefore, does not support the contention that PPD and PPP are distinct syndromes. Nevertheless, this remains an important question as etiologic theories predicated upon aberrations in female reproductive physiology remain an area of active investigation. If a distinct neurobiology of postpartum mental illness or a significantly different prognosis are ever demonstrated, then the current nosology would require modification.

The second question, regarding the 4-week onset window, has drawn increasing criticism. Is postpartum, in fact, a misnomer? Previous studies indicate that depression and anxiety during pregnancy are risk factors for PPD.[28] Instead, we may ask whether this association between prenatal and postnatal depression indicates that the clinical manifestation of depression during the postpartum may represent situational presentations despite the illness having begun in pregnancy.

The 4-week postpartum criteria, largely derived from the literature on severe postnatal illness requiring hospitalization, may not extend far enough postnatally. This is an important clinical consideration since the customary postnatal checkup occurs 6 weeks after delivery. Many women may not see their physician again until a check-up and PAP smear scheduled either 6 or 12 months postpartum. During this 10-month interim, the onus for identification falls to the new mother, her support system, and the pediatrician's office. Consequently, if a substantial number of women with PPD become ill after the 6-week obstetrical visit, this may not be detected for a year unless screening for maternal depression becomes part of the pediatric evaluation during the first postnatal year.

Neurobiology of Postpartum Depression

The temporal association of PPD with childbirth leads to the conclusion that postpartum illness may be precipitated by postnatal changes in female reproductive neuroendocrinology, yet studies investigating biological alterations in PPD are notably negative or lack replication.[41] No confirmed abnormality in the female gonadal axis has been identified; nevertheless, there remains evidence that some may experience PPD as a consequence of differential sensitivity to the dysphoric effects of rapidly changing concentrations of gonadal steroids.[42]

Postpartum autoimmune thyroiditis (PAT) has also garnered attention as a potential cause for PPD.[43,44] Although there appears to be no clear association between thyroid dysfunction and PPD, postpartum thyroiditis may represent a confounding illness that warrants routine postnatal screening. Perinatal screening for thyroid dysfunction is reasonable since the antibody titer for PAT rises during pregnancy and the presence of these antibodies during pregnancy is associated with impaired infant cognition.[45] Such screening should include TSH and free T_4 as well as thyroid antibodies.

It has also been hypothesized that the precipitous decline in maternal circulating concentrations of corticotropin-releasing hormone (CRH) within hours after delivery may contribute to the development of depression during the postpartum.[46] Although this runs counter to the prevailing data indicating that depressed patients hypersecrete CRH in the central nervous system, it is argued that suppression of hypothalamic CRH secretion in the aftermath of the extremely high concentrations of CRH during late gestation increases psychiatric vulnerability.

It must be recognized that the occurrence of mental illness during the postpartum does not mandate a unique

biological etiology. In fact, alternative psychosocial theories involving intrapsychic conflict, personality structure, and psychosocial adaptability have also been postulated.[47,48] A multifactorial etiology may exist in which postpartum illness occurs when the biological alterations of the postpartum are imposed upon an individual with a constitutional vulnerability to illness (i.e., diathesis). Application of such a diathesis/stress model to PPD would account for the fact that the majority of new mothers do not become depressed during the postpartum and would also explain why those who are vulnerable to depression are most likely to become ill at this time.

IMPACT OF EXPOSURE TO POSTPARTUM DEPRESSION UPON OFFSPRING

Children of depressed mothers may be directly and indirectly exposed to maternal illness. An infant's indirect exposure to PPD results from the adverse impact of the illness upon maternal caregiving. More than 4 decades of experience in humans and laboratory animals have documented the long-term adverse consequences of disturbances in maternal care.

Rodent and primate models consistently demonstrate that experimental laboratory stressors interfering with maternal care produce a persistent deleterious impact on offspring. Common stress paradigms include maternal deprivation and variable foraging. Maternal deprivation directly interferes with maternal care by separating the young animal from its mother. Furthermore, maternal deprivation studies routinely demonstrate that maternal care remains aberrant even after reunion.[49] Variable primate foraging paradigms indirectly interfere with maternal care. These studies modulate a naturalistic stressor (e.g., food supply) that does not directly stress the infant but instead increases the work of parenting while permitting adequate nutrition of both mother and infant. The variable foraging model thus provides a vehicle to ascertain the indirect effect of parental stress upon offspring development.[50]

Each of these stress paradigms reliably produces a persistent syndrome of behavioral and neurobiological alterations in the offspring. Offspring behaviors homologous to depression and anxiety in humans persist into adulthood. In addition, these laboratory stressors induce persistent sensitization of the neuroendocrine stress response mediated by the hypothalamic-pituitary-adrenal axis. Interestingly, the only laboratory stressor studied to date that tends to bolster maternal care, i.e., neonatal rat handling,[51–55] typically produces adaptive behavioral effects and reduced neurobiological sensitivity to subsequent stress in the offspring. An upcoming review details how these investigations provide a model of parental depression (D.J.N., Z.N.S., C. B. Nemeroff, M.D., manuscript submitted).

These animal studies are paralleled by clinical research demonstrating the long-term adverse sequelae of aberrant maternal care in humans. It has been 50 years since the deleterious effects of prolonged maternal separation on human infants were first reported by the World Health Organization.[56] For example, extreme social deprivation experienced inside orphanages housing disabled and abandoned children in Romania during the tenure of Ceaucescu resulted in devastating consequences for child development.[57,58]

Subtle deficiencies in maternal care induced by maternal depression also have an adverse impact upon child development. Postpartum depression is associated with disruptive effects on maternal-infant attachment and deficiencies in infant cognitive performance.[59–64] Mildly depressed mothers also demonstrate a decrease in mother-infant behavioral and electrocardiogram synchrony[65,66] as well as depressed infant behavior.[67] Furthermore, depressed mothers tend to perceive their infants in a negative manner and regard their care as more difficult.[63,64] Across a spectrum of severity, maternal mental illness has an adverse impact on the infant and mother-infant interaction.

Breastfeeding infants also may be directly exposed to maternal postpartum depression via breast milk. As previously mentioned, alcohol, nicotine, and medicines present in the breast milk of depressed mothers constitute illness exposure to the infant. In fact, preliminary data from our group indicate that the severity of postpartum depression correlates with alterations in the constituents of breast milk.[68] The relevance of these changes for infant growth and development and whether or not efficacious treatment mitigates these changes remain unknown.

EXPOSURE TO TREATMENT

Treatment Alternatives

Sound treatment decisions are important for women suffering from PPD, particularly given the inherent risk of exposing the child to postpartum illness and the fact that treatment itself poses some degree of exposure. Studies in the treatment of PPD are quite limited relative to the treatment data in other disorders considered specific to women (e.g., premenstrual tension syndrome, premenstrual dysphoric disorder). Review of the extant treatment response literature in postpartum depression reveals a mixture of case series, open trials, and limited randomized clinical investigations that have utilized a variety of inclusion criteria, outcome measures, and interventions. It is reassuring that the vast majority of these studies have shown a positive treatment response, reminiscent of the near global efficacy seen in the earlier noncontrolled investigations in premenstrual dysphoric disorder. These reports are shown in Table 1.

Active therapies. There have been surprisingly few active treatment studies for women with PPD, particularly if documentation of postpartum symptom onset is required. A total of 576 postpartum women with depressive symptoms have been included in investigations of interventional strategies. Numerous psychosocial treatment modalities have

Table 1. Treatment Studies in Women With Postpartum Depression[a]

Type of Study	Design	Sample Size[b]	Postpartum Depression Definition	Control Group	Outcome Measures	Results	Comment	Reference
Active Treatment in Women With PPD								
Drug								
Fluoxetine	Case series	4	DSM-III, onset unknown	None	HAM-D, BDI	All patients made complete recovery (HAM-D < 7, CGI = 1) on treatment with fluoxetine 20 mg/d	2 inpatients, 2 outpatients	105
Sertraline	Prospective, open-label	21	DSM-III, onset < 24 wk postpartum	None	SIGH-D, EPDS, BDI	In 20 women > 50% reduction in SIGH-D scores, 14 women total recovery (SIGH-D < 7, CGI = 1) by 8 wk	Highly efficacious and well-tolerated treatment for women with PPD; suggests earlier symptom onset associated with more rapid response	72
Fluoxetine and/or CBT	Double-blind, placebo-controlled, randomized	61	RDC criteria for minor or major depression at 6–8 wk postpartum	16 fluoxetine + 1 CBT; 13 fluoxetine + 6 CBT; 17 placebo + 1 CBT; 15 placebo + 6 CBT	HAM-D, EPDS	CBT (1 session) and fluoxetine superior to placebo and single counseling session. No significant advantage to combined fluoxetine and CBT (6 sessions)	Both fluoxetine and CBT are effective for PPD; no advantage in combining these therapies	70
Venlafaxine	Prospective, open-label	15	DSM-IV, onset < 12 wk postpartum	None	HAM-D, Kellner Anxiety Scale	Statistically significant change in depression and anxiety by 4 wk. 25% dropout rate	Venlafaxine is effective in treatment of PPD	73
Antidepressants	Retrospective chart review	26	DSM-IV, onset < 4 wk postpartum	25 with nonpostpartum MDE	Treatment course	Women with PPD are more anxious, recover more slowly, and require more medications than controls	Trials are needed to assess anxiety and rapidity of response to medications	106
Psychotherapy								
Social support group	Prospective, controlled	152	CES, EPDS	44 support group; 83 no intervention; 15 information by mail	CES, EPDS	8 social support sessions did not improve mood more than no intervention or info by mail. Multiple measures of adjustment also assessed with no differences	Did not alleviate maternal depression; did increase mother's attention to infant	71
Counseling	Prospective, controlled	41	MADRS > 10; DSM-III-R criteria for MDE, onset unknown	20 counseling; 21 control	MADRS, EPDS	31 women met DSM-III-R criteria, while 41 had MADRS > 10 and were included in analysis. After 6 visits with health nurse, 12 of 15 women with MDE recovered compared with 4 of 16 in control group	Swedish health care system: counseling by health nurses is useful in treating PPD	107
Counseling	Prospective, controlled	50	Goldberg's Standardized Psychiatric Interview, EPDS, symptom onset unknown	26 counseling; 24 control	EPDS		Only 34 women met criteria for major depression at study entry	108
IPT	Prospective, open-trial	6	DSM-III-R criteria for MDE, onset unknown	None	HAM-D, BDI, EPDS	Significant reduction in multiple depression measures after 12 weeks of IPT	Good alternative to medicine, focus on changes in interpersonal relationship postpartum	109
IPT	Prospective, controlled	99	SCID, DSM-IV criteria for MDE	48 active; 51 wait-list control	HAM-D	Significant reduction in depressive symptoms in the IPT group compared with wait-list controls	Approximately $^{2}/_{3}$ of the participants had postpartum onset major depression	69
Other								
Bright light therapy	Case series	2	Clinical diagnosis, onset within 2 wk postpartum	None	HAM-D	75% reduction in HAM-D score		110

cont.

Table 1. Treatment Studies in Women With Postpartum Depression[a] (cont.)

Type of Study	Design	Sample Size[b]	Postpartum Depression Definition	Control Group	Outcome Measures	Results	Comment	Reference
Active Treatment in Women With PPD cont.								
Other								
Transdermal estrogen	Double-blind, placebo-controlled	61	RDC for major depression, onset within 12 wk postpartum	34 active; 27 placebo	Schedule for Affective Disorders and Schizophrenia change, EPDS	17-β estrogen superior to placebo	No evidence of endometrial hyperplasia, 47% of active group taking antidepressants. Dose/duration of treatment guidelines needed	76
Sublingual 17-β estradiol	Case series	2	ICD-10 criteria for PPD	None	MADRS	Both patients' symptoms improved as serum estradiol levels increased. 8 wk of treatment	Subjects had low pretreatment estradiol levels. Estradiol may be related to PPD	78
Sublingual 17-β estradiol	Prospective, open-label	23	ICD-10 criteria for PPD	None	MADRS	Serum estradiol levels increased and MADRS scores decreased by wk 8	Suggests link between low maternal serum estradiol and clinical response to 17-β estradiol treatment	111
Prevention Studies in Women With a History of PPD								
Antidepressants								
Nortriptyline (7), imipramine (2), fluoxetine (4), clomipramine (2)	Prospective, open-label, controlled	23	History of MDE by DSM-III-R during postpartum	15 active; 8 observation	DSM-III-R criteria, IDD	6.7% on antidepressant prophylaxis suffered recurrence compared with 62.5% without medication	Antidepressant treatment effective prophylactic for PPD. Some women on treatment with medications during pregnancy	79
Nortriptyline	Double-blind placebo-controlled, randomized	51	History of PPD, Schedule for Affective Disorders and Schizophrenia with onset within 12 wk	26 active; 25 placebo	RDC criteria for MDE, HAM-D	Nortriptyline does not confer added prevention beyond that of placebo	The rate of relapse in the placebo group was less than would be expected, suggesting benefit from participation and clinical contact	80
Other								
Progesterone	Prospective, controlled	315	History of PPD	94 active; 221 control	Questionnaires to patients and clinicians	Women with history of PPD given progesterone prophylactically; only 9 (10%) had PPD recurrence compared with 68% in untreated group	Progesterone only effective for prophylaxis. Once onset of symptoms, progesterone is ineffective	84
Estrogen	Prospective	11	History of MDE by DSM-III-R, onset within 2 wk postpartum	None	Clinical interview	One woman experienced relapse	Seems to be effective treatment, although study conducted on small sample size	85
Prevention Studies in Community-Based Samples								
Psychosocial								
Antenatal education classes	Prospective, controlled	161	None	85 active; 76 control	Clinician-rated 6-point scale	Only 15% of subjects who took classes had postpartum emotional upset compared with 37% of controls	Women who had their husbands attend class with them did better than those who did not	82
Companionship at birth	Prospective, controlled	189	None	92 active; 97 control	Pitt Depression Inventory		Support during labor and delivery reduced risk of anxiety and depression	81

[a]Abbreviations: BDI = Beck Depression Inventory; CBT = cognitive-behavioral therapy; CES = Current Experiences Scale; CGI = Clinical Global Impressions Scale; EPDS = Edinburgh Postnatal Depression Scale; HAM-D = Hamilton Rating Scale for Depression; ICD-10 = *International Statistical Classification of Diseases*, Tenth Revision; IDD = Inventory to Diagnose Depression; IPT = interpersonal psychotherapy; MADRS = Montgomery-Asberg Depression Rating Scale; MDE = major depressive episode; PPD = postpartum depression; RDC = Research Diagnostic Criteria; SCID = Structured Clinical Interview for DSM-IV; SIGH-D = Structured Interview Guide for the Hamilton Rating Scale for Depression.
[b]Total sample size that completed treatment intervention.

been tested in a series of small community-derived samples. Interpersonal psychotherapy (IPT) is perhaps the best studied psychotherapeutic treatment for women with PPD.[69] IPT addresses the depressive symptomatology as well as the disruption in interpersonal relationships that often accompanies PPD. In a comparison study with fluoxetine, cognitive-behavioral therapy (CBT) proved to be effective for the treatment of postpartum depression.[70] On the other hand, nonstructured social support groups are not effective in treating PPD.[71]

Somatic therapies, such as antidepressants and hormonal supplements, have also been tested in the active treatment of PPD. Trials of sertraline,[72] fluoxetine,[70] and venlafaxine[73] demonstrated their efficacy in the treatment of PPD. The use of gonadal hormones to treat postpartum mood disorders dates back to Schmidt's 1943 report of progesterone treatment for postpartum psychosis.[74] Sublingual and transdermal estrogen have recently been tested in the treatment of PPD.[75–78] Although these reports purported that estrogen treatment was successful, only modest symptomatic relief was provided and, in 1 study, estrogen was accompanied by concomitant administration of an antidepressant.[76] This treatment modality should not be a first-line recommendation due to the limited benefit and lack of safety data regarding the postnatal use of estrogen supplementation in women of reproductive years.

An evaluation of treatment options should include consideration of the time to treatment response. For example, if treatment response is delayed, the infant's exposure to maternal depression is prolonged. Therefore, the use of psychotherapy in order to avoid medication exposure may in fact increase the child's exposure to the illness.

Prevention therapies. Potential strategies for preventing recurrent postpartum depression are emerging as the standard of care in several academic centers that focus on women's mental health. The literature contains 4 investigations of somatic interventions in women (N = 400) with a history of postpartum onset of major depression. In an early open trial, Wisner and Wheeler[79] demonstrated that reintroduction of antidepressants at delivery reduced the risk of recurrent postpartum depression. However, in an elegant, randomized, placebo-controlled trial, the same group failed to demonstrate a significant difference between nortriptyline and placebo.[80] The rate of recurrent PPD in this study was relatively lower than expected in both groups which may have contributed to the results. The issue of regular contact and education in the prevention of recurrent postpartum depression versus an actual relapse rate that is lower than expected based on the rigor of the study design warrants further attention. Psychosocial therapies, including psychoeducation and enhanced social support at delivery, have been associated with decreased rates of depressive and anxiety symptoms in community derived samples (total N = 350)[81,82] and may help reduce the rate of PPD.[83]

Hormonal therapies have also been suggested for PPD prophylaxis. One very large (N = 315), unreplicated study indicates that progesterone therapy may help prevent PPD, though it was not successful as an active treatment once depressive symptoms were evident.[84] A second study indicated that intravenous administration of estrogen (coadministered with heparin for thrombolic prevention) immediately following delivery may prevent the occurrence of PPD in women with a prior history of severe depression.[85]

Interpretation and specific application of the available treatment studies for women with postpartum onset major depression are limited by the few randomized trials and inclusion of women with major depression that may not have started following childbirth. Such comparisons may provide additional information concerning the potentially unique nature of postpartum onset depression. Prophylactic treatment planning should be considered for pregnant or newly delivered women at high risk for PPD. Such planning should include education, assessment of social support, and criteria for intervention as a minimum. Breastfeeding influences choices in both active treatment and prevention planning strategies.

Antidepressants and Lactation

Breastfeeding provides a medium for direct infant exposure to psychotropic medication. Nevertheless, new mothers receive a strong message from a wide array of sources that they should breast-feed. The use of medications during breastfeeding is indeed a significant concern. In the United States, there are approximately 4.2 million live births each year. Nearly half of these women, approximately 2.3 million, are planning to breast-feed.[3] If the rate of PPD is approximately 10%, a conservative estimate, then 230,000 depressed women will be breast-feeding each year. If only 1 in 10 of these women seek psychiatric treatment, nearly 25,000 women will seek physician advice regarding the use of antidepressants during breastfeeding each year.

Exposure terminology. No controlled studies of antidepressant treatment during lactation exist, and it is doubtful there ever will be any. All psychiatric medicines investigated are found in human breast milk.[86,87] The medication concentrations in breast milk (ng/mL) represent relatively low oral doses to the nursing infant; however, the significance of such exposure remains obscure. The breastfeeding baby is exposed to these medications regardless of whether they can be detected in sera or not. The terminology often utilized in breastfeeding studies can be misleading and even frightening. For example, some researchers have described a fear of *accumulation* of fluoxetine in breastfeeding infants,[88] although data supporting the potential for accumulation are limited to case reports. These studies may have simply discovered a higher steady-state concentration, identified infants that are slow metabolizers of the medication, or reported erroneous laboratory

values. *Toxicity* has been used to describe reports in breastfeeding infants of sedation, sleep disturbance, and gastrointestinal distress. Is this truly toxicity or does it represent described medication side effects in the infant? Still other authors[89–92] have described negligible or trace infant exposure. Such terms are without meaning in the absence of any definitive long-term clinical correlation. Until these children reach adulthood and have demonstrated no sequelae of exposure, we cannot with certitude characterize the exposure as negligible. The baby is simply exposed.

Monitoring infant exposure. What is the best means to monitor the medication exposure of a breastfeeding infant? Most researchers have settled upon infant serum concentration of medication as a gold standard for infant monitoring.

Infant serum monitoring appears to be a reasonable approach in the research setting; however, extension to clinical practice is limited. First, most clinical laboratory assays do not have the sensitivity required to detect the typical serum concentrations observed in breastfeeding infants. Consequently, a laboratory report of "undetectable" may convey the false impression that the infant has not been significantly exposed to the medication. "Undetectable" reflects the limits of the assay, and no assay achieves sensitivity to "absolute zero" (Z.N.S., manuscript submitted). Second, in the absence of a meaningful clinical correlation, even a detectable infant serum concentration is not easily interpretable. It is simply a number that at present offers no guidance to clinical decision making. Finally, infant serum concentration may not be the most accurate measure of an infant's true (i.e., functional) medication exposure. Reporting infant serum concentrations in nanograms per milliliter ignores the discrepant potencies of the various antidepressants. For example, the inability to detect paroxetine in the serum of breastfeeding infants[93,94] does not account for the binding affinities. The binding affinity of paroxetine for the serotonin transporter is over 20 times greater than fluoxetine, 10 times greater than citalopram, and 4 times greater than sertraline.[95] Furthermore, this functional exposure should be extended to other sites such as norepinephrine and dopamine transporters to provide a comprehensive picture of infant exposure. Functional exposure via conversion to nanomoles and corrected for the individual medication's binding affinities would provide a rational means, though complex, for comparing the relative exposures to 2 or more medications.

Given these limitations, routine infant serum monitoring is not clinically practical. If there is suspicion that a nursing infant is exhibiting potential medication side effects or the clinician believes there to be side effects, confirmation of a medication mediated event is best done by suspension of the medication exposure. Premature infants, neonates with family histories or evidence of slow metabolism, and infants taking other medications (e.g., reflux, asthma, etc.) represent potential exceptions. The use of antidepressants in breastfeeding women with infants meeting these criteria poses an interesting dilemma. The benefits of breastfeeding may be deemed of seminal importance in these populations. As such, checking infant serum concentration in premature infants (that are often undergoing venipuncture) would appear to be reasonable.

Efforts to provide a means for monitoring infant exposure without performing invasive procedures upon the child have involved the construction and testing of mathematical models derived from pharmacokinetic studies of medication excretion into breast milk[93,96,97] and predictors of infant serum concentrations (Z.N.S., manuscript submitted, and L. S. Cohen, M.D., H. Groninger, B.A., A. Hostetter, B.A., manuscript submitted). These detailed studies have demonstrated that the majority of selective serotonin reuptake inhibitors (SSRIs) peak in breast milk at 7 to 9 hours after maternal dose and "pump and dump" of this peak can result in a 17% to 20% reduction in the total infant daily dose (exposure).

Utilizing this type of model, our group completed a detailed study of both the pharmacokinetics of excretion and infant serum measures for sertraline demonstrating that the maximum calculated infant dose is typically less than 1/400 the maternal dose.[73]

SSRIs in lactation. Numerous groups have reviewed the use of psychotropic medications during lactation.[98–101] The available data regarding SSRIs in lactation now exceeds those of any other class of medication in the *Physicians' Desk Reference* (see Table 2 for summary). Unfortunately, direct comparison or meta-analysis of the breastfeeding studies is complicated secondary to the variation in study methodology and assay sensitivity.

The breastfeeding data regarding SSRIs, nortriptyline,[102,103] and clomipramine[104] have rapidly expanded since the comprehensive review by Wisner and colleagues in 1996.[98] The recent introduction of generic fluoxetine raises an important issue with regard to the reproductive safety of a given compound: are brand name and generic formulations of a compound truly the same? History (for example, the tryptophan experience) suggests that such extrapolation may not be the best treatment alternative. Until further information is available, use of the brand name product represents a relatively safer alternative for both pregnancy and lactation.

CLINICAL APPLICATION OF THE EXPOSURE REDUCTION MODEL

The treatment of PPD raises several key concerns: (1) if exposure to maternal mental illness presents a risk to the infant, is a treatment modality that offers the most rapid remission of symptoms preferred? (2) with the documented efficacy of IPT and CBT, should these psychosocial treatments be preferred for women who choose to continue

Table 2. Studies of Antidepressant Use During Breastfeeding

Medication	Mother Infant Pairs[a] (N)	Mothers Providing Serum Samples (N)	Mothers Providing Breast Milk Samples (N)	Infant Serum Samples Obtained (N)	Adverse Events Reported	Reference
Bupropion	1	1	1	1	1	112
Citalopram	1	1	1	1	None	113
	2	3	3		None	114
	1	1	1	1	1-uneasy sleep	115
	7	7	7	7	None	90
Fluoxetine	1	1	1		None	116
	1	1	1			117
	1	0	1	1	1-crying, emesis, diarrhea, poor sleep, high infant [serum][b]	118
	11	3	11	1[c]	None	119
	4	4	4	2	None	120
	13			13	None	121
	14	14	13	9	1-colic, 1-hyperactive, 2-possible withdrawal	97
	46	39	25	42	None	…[d]
Fluvoxamine	1	1	1		None	122
	1	1	1		None	123
	2	2		2	None	124
	4	2		4	None	125
Nefazodone	2		2		None	126
Paroxetine	1	1	1		None	127
	2			2	None	121
	7	7	7		None	128
	16	14	11	16	None	93
	24	24	24	24	None	94
	16	16		16	None	125
Sertraline	1	1	1	1	None	129
	4	4		4	None	130
	8		8	4	None	131
	3	3		3	None	132
	12	11	12	11	None	96
	9	9		9	None, 1-high infant [serum][b]	133
	3			3	None	121
	10	10	10	10	None	134
	26	22	15	22	None, 1-high infant [serum][b]	…[e]
	30	29		30	None	125
	14	13		11	None	130
Venlafaxine	3	3	3	3	None	135

[a]Total number of mother-infant nursing pairs that involved infant exposure to medication.
[b]High infant serum concentration defined as > 25% of maternal serum concentration.
[c]Urine samples collected from 5 infants.
[d]With permission, from L. S. Cohen, M.D., H. Groninger, B.A., A. Hostetter, B.A., manuscript submitted.
[e]Z.N.S., manuscript submitted.

breast-feeding? and (3) should supraphysiologic doses of estrogen be used to treat PPD in the absence of long-term safety data and relatively modest reductions in depressive symptoms?

These questions are best addressed within the context of a treatment model that considers all aspects of exposure. Maternal depression and/or its treatment results in some degree of exposure, be it to illness or treatment. Exposure cannot be eliminated; it can only be reduced. Therefore, no clinical decision in the context of PPD is ever risk free. The goal of the risk:benefit assessment is to limit exposure either to illness or treatment and help the patient decide which path of exposure is most tolerable for her, her infant, and her family. It is important to conduct a thorough risk:benefit assessment where all treatment options are discussed, as well as the risk of not treating maternal mental illness, with the patient and significant other. During this risk:benefit assessment, the clinician must consider the effects of illness and treatment exposure, not only upon the depressed mother and her infant, but upon the family as a whole, particularly if there are other small children dependent upon active maternal care.

Breastfeeding women should document all medication use (prescription and over-the-counter agents), drug use, and herbal and environmental exposures (e.g., alcohol, tobacco) throughout the course of treatment. To reduce the total number of exposures, we offer the following treatment strategy:

Steps to Reducing Exposure When Treating Postpartum Women With Depression

1. Document all illness exposures: impaired maternal care, medications, alcohol, cigarettes, drugs, and herbal remedies. Encourage the discontinuation of any environmental and nonessential exposures.
2. If clear evidence exists that maternal illness is adversely impacting interaction with infant or other children (e.g., avoidance or overstimulation of neonate, alterations in style of discipline with children), err toward treatment exposure.
3. Guided by the severity of illness, choose a treatment modality that is likely to produce a reliable and timely response.
4. Is appropriate structured psychotherapy (IPT or CBT) available (e.g., insurance coverage, appropriate therapist, geographically and financially feasible)?
5. If a medication is indicated, maximize safety and effectiveness:
   a. Use a medication appropriate for the diagnosis.
   b. Use a medication of prior response. Do not experiment with new medications.
   c. Use a medication of prior infant exposure. Do not switch medications unnecessarily if already used earlier in pregnancy (e.g., medication A in pregnancy + medication B in lactation = no/limited data).
   d. Use a medication with data (e.g., "new and improved" = no/limited data).
   e. Monotherapy at any dose is preferable to introducing a second medication in women that are breast-feeding.
   f. Infant daily dose in breastfeeding with SSRI use can be reduced by "pump and dump" at 8 to 9 hours after maternal medication.
   g. The application of these medication guidelines is based on data derived predominantly from trade name products; data on trade versus generic have not been delineated in previous investigations.
   h. If unsure, get a consultation.
6. Avoid unanticipated exposures: pregnancy is possible when breast-feeding. Consider future pregnancies in treatment planning.

FUTURE DIRECTIONS

Numerous areas in perinatal psychiatric research remain open for investigation. The focus of early detection, to date, has been upon obstetricians, nurse midwives, and lactation consultants. Efforts for identification warrant extension to our colleagues in pediatrics secondary to the greater contact in the first postnatal year. One factor central to future research in postpartum depression is the validity of the nosology of postpartum illness as presented in DSM-IV. Review of the extant literature demonstrates remarkable variability in the symptom onset criteria utilized, which hinders the development of any treatment planning consensus and etiology investigations. Whether postpartum mental illness has a unique treatment response is not presently discernable from the present literature.

Significant advances are needed with respect to formal quantification of infant exposures associated with maternal mental illness. This mandates identification of the neurobiological substrates of PPD and how those substances impact the hormonal, immunologic, and nutritional constituents of breast milk. Furthermore, a better understanding of infant central nervous system vulnerability to both the substrates of maternal illness and the substances employed to treat that illness is needed. With respect to medications in breast milk, this requires working beyond "ng/mL" measures in infant serum and breast milk to a more comprehensive consideration of functional medication exposure. Quantification of functional central nervous system exposure will provide the foundation for much-needed infant follow-up studies. Acquiring infant follow-up data in the context of the impact of stress upon developing neurobiological systems, multiple nonpsychotropic exposures, and the propensity for treatment either to mitigate or potentiate these effects will require collaborative investigations, as no single academic center will be able to amass the requisite sample size. These issues culminate in a seminal clinical concern. Does maternal mental illness during early development represent a child's first adverse life event? Certainly, the burgeoning laboratory data support this contention[4,5] (D.J.N., Z.N.S., C. B. Nemeroff, M.D., manuscript submitted). If so, this may represent a unique opportunity for psychiatry to influence future psychopathologic conditions by providing primary preventative medicine through maternal mental health.

Drug names: bupropion (Wellbutrin and others), citalopram (Celexa), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), nefazodone (Serzone), nortriptyline (Aventyl and others), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

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