Perinatal depression: treatment options and dilemmas

Teri Pearlstein, MD

Department of Psychiatry and Human Behavior, The Warren Alpert Medical School of Brown University and the Women's Behavioral Health Program, Women and Infants Hospital, Providence, RI

The treatment of depression during pregnancy and the postpartum period raises unique concerns about safety for the developing fetus and the infant. An increasing number of studies suggest adverse effects from untreated stress, anxiety and depression as well as adverse effects from antidepressant and other psychotropic medications. Even when studies suggest a lack of short-term adverse effects with some medications, the paucity of systematic longitudinal follow-up studies investigating the development of children exposed to medications during pregnancy and breastfeeding causes apprehension. This review's objective is to highlight what is currently known about the negative effects of untreated disease and exposure to psychotropic medication, the treatment dilemmas confronting women with perinatal depression and issues that future studies should address so that a woman with perinatal depression can make an optimally informed decision.

Le traitement de la dépression au cours de la grossesse et en période post-partum soulève des préoccupations particulières au sujet de la sécurité du fœtus en développement et du nouveau-né. De plus en plus d'études indiquent que le stress, l'anxiété et la dépression non traités ont des effets indésirables, tout comme les antidépresseurs et d'autres psychotropes. Même si des études indiquent que certains médicaments n'ont pas d'effet indésirable à court terme, la rareté des études de suivi longitudinales systématiques sur le développement des enfants exposés à des médicaments in utero et pendant l'allaitement demeure préoccupante. Cette revue vise à cerner les connaissances actuelles des effets négatifs du non-traitement des maladies et de l'exposition aux médicaments psychotropes, les dilemmes auxquels font face les femmes qui ont besoin de traitement pour une dépression périnatale et les questions sur lesquelles les études à venir devraient porter pour que ces femmes puissent prendre une décision éclairée.

Introduction

Women with depression face difficult decisions about treating or not treating their depressive symptoms with medication during pregnancy and while breastfeeding. There are risks to the fetus and infant with exposure to medication as well as with exposure to the underlying untreated disorder. Unfortunately, there are no risk-free options. The safety for the developing child of exposure to antidepressant medication during pregnancy and breastfeeding is an area of current research and great public health significance. This article reviews some of the recent studies and concerns about the potential negative effects of either not treating major depressive disorder (MDD) or of taking psychotropic medication during the perinatal period.

MDD in pregnancy

Diagnosis and epidemiology

The peak prevalence of MDD occurs in women during the reproductive years. Rates of MDD during pregnancy approximate the rates during the reproductive years, (i.e., pregnancy is neither protective nor exacerbating for depressive disorders).[1] Perinatal depression is underrecognized and undertreated in obstetric-gynecological and primary care settings.[2-4] Self-report measures that screen for depression can be used to identify pregnant women who may warrant further assessment for a depressive disorder. In addition, the Edinburgh Postnatal Depression Scale (EPDS),[5] which was developed to identify postpartum depression (PPD), is also commonly

Correspondence to: Dr. T. Pearlstein, Women and Infants Hospital, 101 Dudley St., Providence RI 02905; fax 401 453-7720; Teri_Pearlstein@brown.edu

used to identify depression during pregnancy. It has been suggested that an EPDS score of 15 or more identifies significant depression during pregnancy.[6] The diagnosis of depression in pregnant women can be challenging because some of the diagnostic symptoms of depression overlap with symptoms of normal pregnancy (e.g., sleep or appetite change, fatigue, decreased libido).[7]

One systematic review reported prevalence rates of depression of 7.4% in the first trimester, 12.8% in the second trimester and 12.0% in the third trimester.[8] Another systematic review reported an 11.0% point prevalence of major and minor depression in the first trimester that dropped to 8.5% in the second and third trimesters.[9] Overall, the point prevalence of major and minor depression ranged from 6.5% to 12.9% through pregnancy, while the point prevalence of MDD ranged from 1.0% to 5.6%. The latter study only reviewed studies in which depression was evaluated by structured clinical interview, whereas the former study included studies in which depression was defined by either self-report measures or structured interview. Women with increased risk of elevated depressive symptoms or MDD during pregnancy are often adolescent, unmarried, financially disadvantaged, African-American or Hispanic and lacking in social support; often, they have had a previous depressive episode and recent negative life events.[1]

Untreated depression and pregnancy outcome

Depression, anxiety symptoms and maternal stress can lead to adverse effects in the fetus and offspring. Untreated depression can lead to harmful prenatal health behaviours such as poor nutrition, poor prenatal medical care, smoking, alcohol or other substance misuse and risk of suicide, each of which compromises the health of both the woman and her fetus.[10,11] Untreated depression during pregnancy increases the risk for PPD, which has known negative effects on maternal–infant attachment and child development. In a pregnant woman with depression, the fetus can demonstrate abnormal neurobehavioural responses such as altered heart rate reactivity.[12] Reviews have summarized the numerous adverse obstetric complications reported with untreated prenatal stress and depression.[13–16] These complications include preeclampsia, preterm delivery, low birth weight, miscarriage, small-for-gestational-age babies, low Apgar scores, neonatal complications and high neonatal cortisol levels at birth.[13] However, recent studies have suggested that, with adjustment for potential confounding prenatal variables, untreated depressive symptoms during pregnancy may not be associated with lower birth weight[17] or younger gestational age and preterm delivery.[18] As reviewed, antenatal stress and depression have also been correlated with elevated cortisol levels, language and cognitive impairment, impulsivity, attention-deficit disorder, behavioural dyscontrol and psychopathology in offspring during childhood.[19] A recent study reported that high levels of prenatal anxiety and depression were associated with more sleep problems in children at 18 and 30 months.[20] Hypotheses about the influence of maternal stress and depression on obstetric variables (e.g., preterm delivery) and later childhood development include elevated placental

levels of corticotropin-releasing hormone and cortisol, alterations in immune function, increased catecholamines and uterine vascular changes.[15,16,21–24]

Risk of recurrence with antidepressant discontinuation

To minimize exposure of the fetus to antidepressants, women with prior depression who are doing well on an antidepressant medication may choose to discontinue it before conceiving or once they have conceived. Cohen and colleagues[25] undertook a prospective naturalistic study of women with prior depression who were doing well on an antidepressant at conception. They recently reported that 68% of 44 women who discontinued their antidepressant medication had a relapse of their depression, compared with 26% of 82 women who maintained their antidepressant through pregnancy. A smaller prospective study by Cohen and colleagues[26] reported that 75% of 32 euthymic women with previous depression who discontinued their antidepressant just before or at conception suffered a relapse during pregnancy, mostly during the first trimester. Another study suggested that depressive symptoms may even recur in women who continue antidepressant medication through pregnancy.[27] Thus the risk of depression recurrence is high when euthymic women discontinue antidepressants around the time of conception. If depression recurs, the fetus is then exposed to the negative consequences of untreated depression and anxiety described above.

Antidepressant medication and pregnancy

Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have replaced tricyclic antidepressants (TCAs) as first-line treatments for depression. Because at least one-half of pregnancies are unplanned, women who become pregnant while taking an antidepressant medication are likely to be taking an SSRI or other newer antidepressant. A recent study reported that in 2001 5% of pregnant women in British Columbia had taken an SSRI during pregnancy.[28] Other studies have estimated that up to 9% of pregnant women have been taking an SSRI at some point during their pregnancy.[29–33] These rates suggest that a substantial number of pregnant women take an antidepressant medication for at least a portion of their pregnancy. The fetus is exposed to antidepressant medication through the placenta. SSRIs and their metabolites have been detected in both umbilical cord blood and amniotic fluid, with ratios of cord blood to maternal serum concentrations ranging from 0.29 to 0.89.[34] Ratios closer to 1 suggest increased fetal exposure to a drug, relative to maternal serum levels, and higher fetal levels may contribute to neonatal complications.[34–36] However, fetal drug exposure is determined by factors additional to maternal serum concentration, and current research is examining the role of fetal genotypes for drug metabolism and transporter proteins located in the placenta.[36,37]

Miscarriage and birth outcome

A recent meta-analysis reported a significant odds ratio of 1.7

for spontaneous miscarriage with SSRI use.[38] Another recent meta-analysis similarly concluded that, compared with nonexposure, maternal exposure to antidepressant medication was associated with a 1.45 relative risk of spontaneous miscarriage; however, the spontaneous miscarriage rate of 12.4% with exposure was within the range of normal population rates.[39]

Studies of the influence of SSRI exposure on birth outcomes have yielded mixed results. Lower birth weight, younger gestational age at birth and lower Apgar scores have been reported with SSRI exposure, compared with TCA exposure or no exposure,[40] and with third-trimester exposure to fluoxetine, compared with first- or second-trimester exposure.[41] Lower birth weight has been associated with higher dosages of fluoxetine in comparison with lower dosages or with other SSRIs.[42] A retrospective review of records of a Canadian population cohort reported that maternal use of SSRIs increased the risk of low birth weight, preterm birth, fetal death and seizures in infants in comparison with infants born to mothers without SSRI exposure.[43] However, other studies have failed to find birth weight differences between infants with early and late exposure to SSRIs[44,45] or between infants exposed to SSRIs and nonexposed infants.[46,47]

Many of the studies examining miscarriage rates and birth outcomes have not controlled for untreated maternal depression, concomitant medications, smoking, alcohol or drug misuse, reproductive history, maternal age or other sociodemographic variables. A recent study compared infants exposed prenatally to SSRIs with infants of mothers with untreated depression and infants of healthy control subjects and reported that prenatal exposure to SSRIs was associated with lower gestational age at birth and increased risk of preterm birth, but not with lower birth weight or lower Apgar scores.[18] Another recent, large study of more than 119 000 births compared birth outcomes of infants whose mothers suffered from depression treated with SSRIs, infants whose mothers had depression not treated with SSRIs and infants of nonexposed control mothers while controlling for the severity level of maternal depression.[28] Compared with infants of mothers whose depression was not treated with SSRIs, infants of SSRI-treated mothers were more likely to have lower birth weight and younger gestational age; moreover, a higher proportion were born at less than 37 weeks. When maternal illness severity was controlled for, maternal depression and SSRI use were significantly associated with increased incidence of birth weight below the 10th percentile. The compelling results of this study of a large sample of birth outcomes suggest that exposure to SSRIs adds to the negative birth outcomes (lower birth weight and younger gestational age) that are due to the effect of exposure to underlying depression alone.[28]

Congenital malformations

Several studies have examined rates of congenital malformations associated with exposure to antidepressants during pregnancy and compared them with rates in the general population. One recent meta-analysis reported that SSRIs were not associated with an increased risk of major or minor malformations.[38] Another recent meta-analysis involving 7 prospective studies and 1774 cases reported that newer antidepressants as a group were not associated with a risk of major malformations above the 1%–3% population baseline risk.[48] However, a recent study of teratogenicity data from 151 800 births in Denmark reported that 4.9% of children born to mothers who took SSRIs early in pregnancy had congenital malformations, compared with 3.4% of children born to mothers who did not take SSRIs during pregnancy, yielding a 1.34 increased relative risk.[49] The common malformation types were cardiovascular (29%), muscle and bone (31%) and digestive organ (14%). As in many studies, this study did not control for underlying maternal psychiatric disease. Two recently published large case–control studies have reported a small increased risk of omphalocele, craniosynostosis and anencephaly with early-pregnancy use of SSRIs as a group,[50] as well as an association of sertraline with omphalocele and of paroxetine with right ventricular outflow tract obstruction defects.[51] However, the absolute risks were low. Other studies have reported a lack of elevated congenital malformation rates with exposure to fluoxetine[41,42,52–54] or with exposure to sertraline, paroxetine, fluvoxamine and citalopram.[42,46,54–56]

With regard to paroxetine, a retrospective study reported an increased risk of 2.2 for overall major congenital malformations and an increased risk of 2.08 for cardiovascular malformations (mostly ventricular septal defects), compared with other antidepressants. In 2005, given these results, GlaxoSmithKline added a warning to the paroxetine label concerning its use in pregnancy.[57] In December 2005, the Food and Drug Administration (FDA) issued a public health advisory about paroxetine use in pregnancy, and paroxetine's FDA pregnancy category was changed from C to D. Another retrospective cohort study[58] and a recent meta-analysis[59] have confirmed the increased risk of cardiac malformations with paroxetine use in the first trimester. However, a recent study of teratology information services reported that paroxetine was not associated with increased risk of cardiovascular defects after first-trimester use.[60] An absence of increased risk for congenital malformations has been reported with TCAs,[61] venlafaxine,[62] mirtazapine,[63] bupropion,[64,65] trazodone and nefazodone.[66]

Neonatal behavioural syndrome

A neonatal behavioural syndrome, also termed neonatal toxicity, poor neonatal adaptation and neonatal abstinence syndrome, has been described in a proportion of neonates exposed to antidepressants in the third trimester. A comprehensive review of cohort studies and case studies reported that SSRI exposure in late pregnancy carries an overall risk ratio of 3.0, compared with first-trimester exposure or no exposure.[67] A recent study estimated that neonatal behavioural symptoms occur in 30% of neonates.[68] The behavioural syndrome includes jitteriness, poor muscle tone, weak or absent cry, respiratory distress, hypoglycemia, low Apgar score and possible seizures.[69,70] The symptoms are usually mild and transient, but supportive care in special care nurseries may be indicated.[55,67,71] A recent study reported that 15.7% of infants born to mothers who took SSRIs during the third trimester were treated in special or intensive care units, compared with 11.2% of infants ex-

posed during the first trimester only; however, the neonatal symptoms associated with stay in special care units were not identified.[44] The recent large study of more than 119 000 births mentioned above also reported that infants of mothers whose depression was treated with SSRIs were significantly more likely to have respiratory distress at birth.[28]

Examination of adverse event reactions in the World Health Organization database (over 3 million case records)[72] and a comprehensive literature review[67] have indicated that neonatal behavioural symptoms are particularly associated with paroxetine and fluoxetine. Additional cases of neonatal symptoms have been recently reported with third-trimester use of venlafaxine,[73,74] citalopram[55,75] and paroxetine.[76] The signs and symptoms of the neonatal behavioural syndrome have not been consistently characterized, but they are similar to signs and symptoms of adult serotonin toxicity, SSRI discontinuation syndrome and cholinergic overdrive.[67,69,70,77] More study of the neonatal symptoms is needed because studies to date have not included blinded infant assessments, use of an established neonatal behavioural symptom scale, control for maternal variables and systematic follow-up to evaluate long-term sequelae.[78] Neonatal jitteriness, irritability, respiratory difficulties, poor suck reflex, urinary retention, functional bowel obstruction and, rarely, seizures have also been described with third-trimester TCA use.[10,35] In 2005, the FDA suggested that an advisory about the potential for neonatal symptoms with late third-trimester use be included in antidepressant prescribing information.

Persistent pulmonary hypertension in the newborn

In early 2006, a case–control study suggested an association between SSRI use after week 20 of pregnancy and an increased risk of persistent pulmonary hypertension of the newborn (PPHN).[31] The normal risk of PPHN in newborns is 1/700; with SSRI exposure after week 20, this was raised to 7/1000 with controlling for maternal body mass index, diabetes, nonsteroidal anti-inflammatory drug use and smoking. Although the increase in absolute risk is small, it is of concern because PPHN can be fatal in 10%–20% of newborns. The authors suggested that SSRIs might promote pulmonary artery constriction after birth by inhibiting the vasodilator nitric oxide or by direct effects on pulmonary smooth muscle cells.[31] However, these theories of SSRI pulmonary effects have been challenged.[79,80] The authors also suggested that PPHN might fall on the severe end of the spectrum of various respiratory and hypoxic neonatal behavioural symptoms associated with third-trimester SSRI use.[31] Notably, the increased risk of PPHN was not associated with SSRI use at any point in the pregnancy, and SSRI use before week 20 approached significance as a protective factor against PPHN.[31] In July 2006, the FDA issued an alert about the increased risk of PPHN with SSRI use in the second half of pregnancy .

Long-term effects of antidepressant medications during pregnancy

There are few longitudinal studies examining the cognitive, neurologic and behavioural status of children exposed to untreated disease or antidepressant medications during pregnancy. Reports of altered cord blood serotonin metabolites,[81] decreased whole blood serotonin levels and platelet serotonin uptake[82] and increased tremulousness and altered sleep organization in neonates,[83] as well as blunted pain responses in 2-month-old infants,[84] raise concerns about possible long-term effects of SSRI exposure during pregnancy on neurotransmitter function. Two studies in a cohort of 4-year-old children recently reported that current maternal depression, but not exposure to SSRIs during pregnancy, was associated with internalizing (i.e., emotional reactivity, depression, withdrawal and anxiety)[85] and externalizing (i.e., increased activity and aggression)[86] behaviours. A review of previous studies of the long-term development of children with prenatal or postnatal SSRI exposure, or both, identified 11 studies (306 children) demonstrating no impairment with exposure and 2 studies (81 children) suggesting mild adverse effects.[87] Normal neurodevelopment, language development and IQ were reported in prospective cohorts of children up to age 5 years exposed to TCAs or fluoxetine, compared with children having no exposure.[88,89] Normal neurodevelopment at 1 year was also reported in a prospective study of infants with fetal exposure to citalopram who were compared with nonexposed infants.[90] One of the 2 studies suggesting mild adverse development in children with SSRI exposure was prospective, suggesting subtle slowed motor development and motor control in comparison with the children of mothers with depression who elected not to take medication.[91] The other study was retrospective, reporting abnormal psychomotor development testing in children aged 7–10 months who were previously exposed to antidepressants, compared with nonexposed children.[92] Further systematic studies of the long-term developmental effects of exposure to both untreated illness and antidepressant medication are needed.

Anxiolytic medications and pregnancy

Benzodiazepines are sometimes used in pregnancy as adjunctive treatments for comorbid anxiety or insomnia. A case–control study of 22 865 infants with congenital abnormalities who were compared with 38 151 infants without congenital abnormalities did not reveal an association between first-trimester exposure to benzodiazepines and teratogenic risk.[93] However, meta-analyses of studies have identified a small increased risk of oral cleft with in utero exposure to benzodiazepines.[61,94] A recent study reported that first-trimester benzodiazepine exposure was associated with pylorostenosis and alimentary tract atresia, premature birth and low birth weight, but not with orofacial clefts.[95] It has been recommended that benzodiazepine use be avoided during the first trimester organogenesis period, if possible. If anxiolytics are used, shorter half-life benzodiazepines, monotherapy, the lowest possible dosage and divided doses should be considered.[96]

Floppy infant syndrome and benzodiazepine withdrawal are 2 types of potential neonatal complications with third-trimester use of benzodiazepines. Floppy infant syndrome is

characterized by hypothermia, lethargy, feeding difficulties, and poor respiratory effort.[96,97] Symptoms of neonatal benzodiazepine withdrawal, which may persist for weeks, include irritability, hyperreflexia, hypertonia, restlessness, abnormal sleep patterns, diarrhea, vomiting, apnea, tremors or jerking of the extremities and suckling difficulties.[96,97] It was recently reported that the combined use of clonazepam and paroxetine during the third trimester led to more problematic neonatal symptoms than the use of paroxetine alone, possibly owing to increased serum levels of both medications.[98] This study suggested that caution is indicated when an adjunctive benzodiazepine is combined with an SSRI. Neonatal symptoms need to be monitored if maternal use of benzodiazepines has occurred proximate to delivery, and slow tapering of benzodiazepines before delivery is prudent if clinically tolerated.[97] Both developmental delays and normal neurobehavioural development have been reported, but few studies have been conducted on the long-term development of children exposed to benzodiazepines during pregnancy.[97,99]

Mood stabilizers and pregnancy

Lithium and the antiepileptic medications may be used in the treatment of manic symptoms, psychotic symptoms and severe depression. The primary concern about lithium use during pregnancy is that with first-trimester exposure the risk of cardiac anomalies, specifically, Ebstein's anomaly, increases from a risk of 1:2000 (0.05%) to 1:1000 (0.1%).[100] Level II ultrasonography at 16–18 weeks' gestation assesses cardiac anomalies. The small but increased absolute risk must be weighed against the risk of untreated or suboptimally treated manic or psychotic symptoms. As pregnancy progresses, it may be necessary to increase the dose and frequency of lithium dosing to maintain stable serum levels.[101,102] Recent guidelines suggest suspending lithium before delivery to avoid maternal toxicity with the rapid decrease in vascular volume at delivery; however, immediately after delivery, the dosage should be increased and serum levels monitored to help prevent postpartum relapse.[103] Neonatal effects in infants exposed to lithium include hypotonicity and cyanosis and floppy infant syndrome. Third-trimester lithium use can lead to neonatal diabetes insipidus, hypothyroidism, low muscle tone, lethargy, hepatic abnormalities, respiratory difficulties and polyhydramnios, but these complications are rare.[102,103] Minimal data exist, but there have been no reported negative long-term consequences for child neurobehavioural development after gestational lithium exposure.

First-trimester exposure to carbamazepine carries an elevated 0.5%–1% risk of neural tube defects as well as increased risks of craniofacial abnormalities, fingernail hypoplasia and growth retardation.[102,104] Lower birth weight and decreased head circumference have also been noted. Teratogenicity is increased when carbamazepine is given with other antiepileptics, particularly valproate. Few adverse reports of neonatal toxicity have appeared in the literature, and further studies examining long-term neurobehavioural development in children exposed to carbamazepine are needed.

The teratogenic risks associated with valproate are more serious. Several reviews of studies have identified an association between valproate and a greater incidence of major congenital abnormalities than has been found with the other antiepileptics, particularly at dosages above 800–1000 mg daily.[105–108] Neural tube defects occur in 5%–9% of neonates after first-trimester exposure.[102,109] A fetal valproate syndrome has been described that includes craniofacial abnormalities, cardiovascular abnormalities and developmental delay.[104,110] Neonatal toxicity includes decelerations in heart rate, liver toxicity, hypoglycemia, reduced fibrinogen levels, jitteriness, difficulty feeding and abnormal tone.[102,109] Valproate should be administered in divided doses, and serum valproate levels should be monitored.[108] Studies suggesting lower intelligence in children exposed to valproate during pregnancy need to be replicated.[105,111–113]

With both carbamazepine and valproate, fetal ultrasonography and a test for serum α-fetoprotein level can screen for a neural tube defect.[101,114] Supplemental folic acid (3–5 mg daily) is recommended before conception occurs (ideally) and through at least the first trimester.[112,115] However, it has not been clearly demonstrated that folic acid supplementation reduces the risk of neural tube defects in pregnant women taking anticonvulsants. Vitamin K 20 mg daily is recommended in the last month of pregnancy to avoid a bleeding diathesis.[115] Much of the teratogenic data collected in the past on carbamazepine and valproate preceded current prenatal screening and folate supplementation guidelines. Results from current prospective registries such as the International Registry of Antiepileptic Drugs and Pregnancy may yield new data about the safety of antiepileptic drugs during pregnancy.[116]

Lamotrigine is an antiepileptic drug with known benefit for the maintenance treatment of bipolar disorder; it also shows promise for treatment of rapid-cycling bipolar disorder and bipolar depressive episodes. Lamotrigine monotherapy is associated with a 2%–3% risk of congenital malformations, which is similar to the risk rate in the general population.[106,107,117,118] There is a possibility that, as with valproate, malformations are more likely to occur at higher maternal dosages.[106] However, a recent report from the International Lamotrigine Pregnancy Registry refuted an effect of lamotrigine dosage on rates of birth defects.[117] There are as yet no consistent data on specific malformation clusters, intrauterine growth effects or neurobehavioural toxicity, but an association of first-trimester exposure with nonsyndromic cleft palate deformity has recently been suggested.[108] Infants with antigen characteristics that differ from those of the mother have a risk for hepatotoxicity and skin rash.[102,109] Minimal safety data are available for topiramate, gabapentin, levetiracetam and oxcarbazepine. Studies suggest that antiepileptic monotherapy appears to decrease the teratogenic risks in comparison with multiple antiepileptics.[107,108]

Antipsychotics and pregnancy

During pregnancy, antipsychotics may be administered for psychosis, bipolar disorder or severe agitation. Reviews of studies involving haloperidol (a butyrophenone) have not suggested increased rates of congenital malformations,[119–121]

although case reports of limb defects have led to the suggestion of a first-trimester ultrasonograph with haloperidol use.[122] The findings with phenothiazines have been mixed.[119–121] A meta-analysis of first-trimester phenothiazine exposure reported a small increase in the relative risk of congenital anomalies (2.4%) relative to the 2.0% risk in the general population, particularly with phenothiazines having aliphatic side chains (e.g., chlorpromazine).[61] The use of traditional antipsychotics at the end of the third trimester has been associated with neonatal dyskinesias, tremor, motor restlessness, hypertonicity, difficulty with oral feeding, apathy and cholestatic jaundice.[119,120,123] Adverse long-term effects on behavioural and cognitive functioning in children with in utero traditional antipsychotic exposure have not been identified to date, but the data are limited.[119,120]

The newer "atypical" antipsychotics (i.e., clozapine, olanzapine, risperidone, quetiapine, aripiprazole and ziprasidone) are now used more frequently than traditional antipsychotics owing to their greater tolerability and decreased risk for tardive dyskinesia. However, the side effect profiles of some of the newer antipsychotics are problematic (e.g., weight gain and glucose intolerance), and they should be discussed with the patient, particularly in the context of pregnancy.[124] A recent prospective cohort study of 151 infants with first-trimester exposure to olanzapine, risperidone, quetiapine and clozapine did not reveal an increased risk of major malformations in comparison with a nonexposed group.[125] However, women with first-trimester use of these medications did have babies with lower birth weight and had higher rates of therapeutic abortions than the comparison group.[125] A recent review confirms the lack of congenital abnormalities reported with olanzapine, risperidone and clozapine to date[119]; however, other reports have reported slightly higher malformation rates with olanzapine and clozapine.[126–128] Recent case reports have described healthy births of infants exposed to aripiprazole[129,130] and quetiapine.[131] No published data exist to date on effects of in utero exposure to ziprasidone. Neonatal shoulder dystocia and seizures have been reported with clozapine use before delivery.[119,124] It has been suggested that infants exposed in utero to clozapine should have a complete blood count obtained to rule out agranulocytosis.[126,128] A recent report suggests that olanzapine may be associated with higher rates of low birth weight and admission to neonatal intensive care units.[36] Studies are needed on the long-term effects on child development of atypical antipsychotic use during pregnancy.

Nonpharmacologic treatments and pregnancy

Psychotherapy can be an initial or adjunctive treatment choice for a pregnant woman with depression. A recent meta-analysis identified several psychotherapies routinely used for MDD that have a moderate effect size in perinatal depression.[132] Few studies have systematically evaluated psychotherapy in pregnant women with depression, but a randomized controlled study of interpersonal psychotherapy (IPT) reported that a 16-week program of group IPT was superior to a parenting education program in improving Hamilton Depression Rating

Scale (HAMD),[133] EPDS and Clinical Global Impression Improvement (CGI-I)[134] scores in pregnant women suffering from depression.[135] IPT is an established treatment for PPD,[136] and its attention to role transitions and interpersonal issues make it an excellent short-term therapy choice for pregnant women with depression, as well. Two small, open studies of individual IPT in pregnant women have also reported positive results.[137,138] Randomized trials have suggested that bright light therapy,[139] massage[140] and acupuncture[141] have efficacy for depression during pregnancy. A recent small study reported that omega-3 fatty acids were superior to placebo for depression during pregnancy.[142] Although not specifically studied in pregnant women with depression, moderate exercise is noted to improve maternal well-being without adverse effects on birth outcomes.[143] A case report described the successful use of vagus nerve stimulation for depression through pregnancy, labour and delivery.[144] Severe depressions not responsive to pharmacotherapy or nonpharmacologic treatments may be responsive to electroconvulsive therapy. Although electroconvulsive therapy has been used safely in pregnancy, specific maternal and fetal precautions need to be implemented.[145]

Treatment dilemmas for pregnant women with MDD

Given the growing evidence that depression, stress, anxiety and psychotropic medications all involve fetal exposure, pregnant women with depression face significant treatment dilemmas (Box 1). A woman who is doing well on her antidepressant may wish to taper it to decrease the exposure of the fetus to medication, particularly during the first trimester, when organogenesis occurs. However, the risk for relapse of MDD is high, and the woman needs to be monitored for relapse. Cohen and colleagues[25] reported that 60% of women who had suffered a relapse after discontinuing their antidepressant restarted their antidepressant during the pregnancy. In an editorial, Rubinow[146] recently posed the question as to whether a 68% likelihood of depressive relapse in untreated women with recurrent depression is worth a 6-fold decrease in the risk of a condition that occurs in 1/1000 infants (i.e., PPHN). Women with severe symptoms who choose to remain medication-free need frequent monitoring and an established safety plan.[147] If a pregnant woman decides to start or continue medication, monotherapy and the minimum effective dosage of an antidepressant without known teratogenicity should be used. The dosages of medications may need to be increased as the pregnancy progresses, owing to altered serum levels arising from changes in plasma volume and changes in metabolism.[10] Women who have remained on medication through their pregnancy and are doing well face the dilemma of whether or not to taper antidepressant medication before delivery in an attempt to decrease a possible neonatal behavioural syndrome. Such a taper may predispose a woman to an increased risk of depression before delivery and postpartum, the timing of delivery is imprecise, and the benefit to neonates of such a taper has not been established.[67] Factors that govern the selection of treatment options include the patient's psychiatric history and response to treatment, plans for breastfeeding, the clinician's

presentation of treatment choices with their risks and benefits, the patient's perception of the treatment choices with their risks and benefits and, finally, cultural expectations.[148,149]

Postpartum depression

Postpartum blues

Postpartum blues occur in 15%–85% of women, peaking at day 5 and usually resolving by days 7–10.[150] In addition to mood swings, irritability, tearfulness, fatigue and confusion, mild hypomanic symptoms and elation may also occur.[150–152] A review of risk factors for postpartum blues suggested that neuroticism, depression during pregnancy, prior nonpuerperal depression and prior premenstrual depression were predictive of early mood changes.[150] Since this review, a study has reported that significant risk factors for postpartum depressive symptoms during the first 3 days after delivery included low mood during the third trimester of pregnancy, prior premenstrual dysphoric disorder and prior MDD including PPD.[153] Another study identified immigration within the last 5 years, previous

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Box 1: Risks associated with depression and psychotropic medications during pregnancy

Untreated stress, anxiety and depression
- Obstetric complications (e.g. low birth weight, preterm delivery, preeclampsia)
- Elevated cortisol levels, cognitive impairment, impulsivity, aggressive behaviours, dysphoria and attention-deficit disorder in children

Antidepressants: selective serotonin reuptake inhibitors
- Slight increase in rate of spontaneous miscarriages
- Possible increased risk of cardiac congenital malformations with paroxetine
- Lower birth weight or premature birth
- Persistent pulmonary hypertension of the newborn with selective serotonin reuptake inhibitors after week 20
- Transient neonatal adaptation symptoms (e.g., jitteriness, respiratory distress, poor feeding)

Antipsychotics
- Possible small increased risk of congenital malformations
- Transient neonatal effects

Lithium
- Increased risk of Ebstein s cardiac malformation
- Floppy infant syndrome (neonatal hypotonicity, cyanosis, feeding difficulties)
- Rare hypothyroidism, diabetes insipidus, polyhydramnios

Carbamazepine
- Spina bifida, craniofacial abnormalities, growth retardation

Valproate
- Spina bifida, craniofacial abnormalities, cardiovascular abnormalities, developmental delay
- Transient neonatal effects
- Possible lower intelligence in children

Lamotrigine
- Possible nonsyndromal cleft palate

Benzodiazepines
- Possible small increased risk of oral cleft
- Floppy infant syndrome (neonatal hypotonicity, cyanosis, feeding difficulties)
- Neonatal benzodiazepine withdrawal
- Possible developmental delay in children

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nonpuerperal MDD, preeclampsia, stressful life events, lack of perceived support, vulnerable personality style, lack of readiness for hospital discharge and dissatisfaction with infant feeding method as predictors of depressive symptoms at 1 week postpartum.[154] Many biological measures, such as decreased allopregnanolone[155] and decreased brain tryptophan availability,[156] have been examined in women with postpartum blues, but no definite associations have been identified.[150] Although postpartum blues are transient and do not require intervention, they are important because postpartum blues are a risk factor for subsequent PPD.[157]

Prevalence of PPD

Gavin and colleagues' systematic review[9] of studies that determined depression by structured interview estimated that the point prevalence of MDD ranged from 1.0% to 5.7% through the first 6 months postpartum, peaking at 3 months postdelivery, and that most episodes occurred with postpartum onset. The point prevalence of major and minor depression ranged from 6.5% to 12.9% through the first 6 months postpartum. A recent large cohort study conducted in Denmark reported that the first 90 days postpartum represent a time of increased risk for new-onset psychiatric disorder, inpatient admission and outpatient treatment in new mothers but not in new fathers.[158] PPD was the most common new-onset psychiatric disorder in these new mothers. Examinations of sibling pairs have suggested a familial and genetic contribution to the development of PPD.[159–161]

The EPDS is the most extensively studied screening measure,[162] and a score of 13 or higher indicates probable PPD.[6] The EPDS scale measures anxiety symptoms as well as depressive symptoms, and reviews suggest a high false-positive screening rate.[7,162] Other depression screening measures are also useful, and the optimal time to screen for PPD appears to be between 2 weeks and 6 months after delivery.[162] Prevalence rates vary worldwide, and some cultures report predominantly somatic symptoms.[163] Because postpartum bipolar disorder can present as depression, it is important to screen postpartum women for hypomanic and manic symptoms.[147,164] Although suicide and infanticide are not common, women being evaluated for PPD should be screened for thoughts about harm to themselves or others.[165,166]

PPD is underrecognized and undertreated,[5,162] probably even more than MDD is underrecognized and undertreated when not related to pregnancy. Postpartum women with depression are often reluctant to discuss their symptoms with their primary care provider, obstetrician or child's pediatrician. Reasons include fears of being seen as a "bad" mother, fears that they are "crazy" and the stigma associated with having a psychiatric problem.[167] Well-child visits with a pediatrician and the postpartum gynecological visit are the opportunities for the detection of PPD.[168,169] Multiple barriers exist to screening for psychiatric disorders in medical care settings; they include time constraints, clinician discomfort with psychiatric disorders and lack of knowledge about resources.[170] Even when women are identified and referred for treatment with mental health providers, compliance with

treatment can be poor owing to minimal time for self because of the demands of newborn care, cost of treatment, lack of childcare, lack of transportation or a mismatch between a woman's background and needs and recommended services.[167]

PPD comprises MDD with postpartum onset (the most stringent definition), MDD that began during pregnancy and continues postpartum or MDD in which atypical symptoms predominate; the significance of these differences is unclear.[171,172] In addition, some women have depression during pregnancy that improves postpartum.[173,174] Postpartum women also have high rates of comorbid anxiety and obsessive symptoms.[175–178] It has been suggested that altered cortisol levels and hypothalamo-pituitary-adrenal (HPA) function as well as genetic polymorphisms may underlie the course of perinatal mood and anxiety symptoms.[171]

Reviews have extensively examined risk factors for PPD.[179] It has been suggested that at least a subgroup of women who develop PPD have a differential sensitivity to hormonal fluctuations. Bloch and colleagues induced hypogonadism in 16 euthymic women, 8 with previous PPD and 8 without a psychiatric history.[180] Supraphysiologic dosages of estradiol and progesterone were added back for 8 weeks and then withdrawn for 4 weeks under double-blind conditions. Five of the 8 women with prior PPD developed mood symptoms during both the hormone replacement and withdrawal phases, compared with none of the 8 women without prior MDD. A recent study reported an association between MDD and higher levels of estrogen on the third day postpartum, compared with levels in healthy control subjects and in women with previous MDD.[181] A recent prospective study of women who were at high risk for PPD reported that PPD was more likely to occur with prior premenstrual dysphoric disorder, prior MDD, mood symptoms with past oral contraceptive use and mood symptoms in the first 2–4 days postpartum.[182] Besides sensitivity to estrogen and progesterone fluctuations at parturition, other biological theories have included altered platelet serotonin transporter binding,[183] fluctuations of other gonadal hormonal and neuroactive steroid levels after delivery, altered levels of cortisol and other HPA axis parameters, altered oxytocin and arginine vasopressin levels, altered fatty acid status and brain neurobiological changes.[184–187] Sleep disturbance in infants has been described as both a risk factor for and outcome of PPD.[188,189] Psychosocial risk factors include previous depression, depression during pregnancy, anxiety during pregnancy, stressful life events during pregnancy or the early puerperium, poor social support, marital conflict, vulnerable personality and immigrant status.[179,190–192]

Risks to offspring of not treating PPD

PPD is associated with marital relationship disruption, low self-esteem, impaired social functioning, impaired occupational functioning and poor quality of life.[193–195] There is clear and abundant evidence of an association between maternal depression and impaired child development.[196–199] PPD is associated with negative effects on maternal–infant interactions such as maternal withdrawal, disengagement, hostility and intrusion.[200–202] PPD also leads to poor cognitive functioning, emotional maladjustment and behavioural maladjustment in infants and children.[85,203–207] Untreated maternal depression that persists can lead to externalizing disorders (e.g., conduct disorders) and violent behaviour[86,208–211] and to psychiatric and medical disorders in adolescence and the early 20s.[212] It is critical to treat PPD because of the deleterious effects on mother, infant and other family members.

Prevention studies

Several reviews of psychotherapeutic and pharmacologic regimens for the prevention of PPD have been recently published; each notes the lack of clearly effective interventions to prevent PPD.[213–218] Many prevention studies have had methodological limitations and have not been conducted in high-risk pregnant women. A small pilot study reported superior efficacy of sertraline, compared with placebo, in preventing the onset of PPD in 22 women with previous PPD.[219] A recent study reported that a group intervention based on IPT principles was superior to standard antenatal care in preventing the occurrence of PPD in 99 financially disadvantaged women at risk for developing PPD.[220] Postpartum administration of progesterone and postpartum debriefing may have harmful effects. Sertraline, high-dose estrogen, mother-to-mother peer support, brief inpatient cognitive-behavioural therapy (CBT), group IPT, prenatal couples classes, minimizing sleep deprivation and intensive midwife-managed care deserve further study.[189,213]

Treatment of PPD

There have been few treatment studies conducted with antidepressant medication in women with PPD, and no antidepressant medication is FDA-approved for PPD. Breastfeeding women have been excluded from many of the existing studies. It is assumed that medications that are effective for nonpuerperal MDD are also effective for PPD, although this assumption has not been studied systematically. Some aspects of PPD are unique, such as postpartum hormonal fluctuations, the possible influence of breastfeeding on mood, sleep deprivation and new stresses occuring with a newborn. Even though the administration of placebo to women with PPD poses ethical dilemmas, given the known negative effects of PPD on child development, placebo-controlled studies are needed to establish the efficacy of pharmacologic treatments for PPD.

Antidepressant treatment

One placebo-controlled antidepressant treatment trial for PPD compared fluoxetine with supportive counselling in 87 postpartum women with major or minor depression.[221] Women who were breastfeeding or who had depression of more than 2 years' duration or whose symptoms were severe enough to "require close monitoring or hospitalization" were excluded. Women were randomized to receive fluoxetine 20 mg daily and 1 counselling session, fluoxetine 20 mg daily and 6 counselling sessions, placebo and 1 counselling session or placebo

and 6 counselling sessions. Among the 61 women who completed the 3-month study, fluoxetine was superior to placebo according to the HAMD (mean scores decreased from 13.3 to 2.9 with fluoxetine, compared with a decrease from 14.0 to 5.4 with placebo). Six sessions of counselling were significantly superior to a single session according to HAMD scores (which decreased from mean 13.3 to 3.2 with 6 sessions, compared with a decrease from 14.0 to 4.8 with 1 session). There was no advantage of combined fluoxetine and counselling over either treatment alone. The pretreatment HAMD and EPDS scores were both in the range for mild depression. Another recently published placebo-controlled antidepressant study reported that immediate-release paroxetine was superior to placebo in 70 women with PPD.[222]

A recent study compared sertraline and nortriptyline in a flexible-dose regimen over 8 weeks in 109 women with PPD (HAMD-17 item score > 18 at baseline).[223] After either 4 or 8 weeks, no differences were observed between sertraline and nortriptyline in the proportion that responded (defined as a 50% reduction in HAMD score) or remitted (HAMD score ≤ 7); by week 8, almost one-half of the full sample had remitted on either medication. Although the side effects in the subjects differed by medication, the burden of side effects was similar. About 45% of subjects were breastfeeding (Dr. K. Wisner, University of Pittsburgh School of Medicine, personal communication, 2008). Infant serum levels were near or below detectable levels, and no adverse effects in the infants were reported.[223] The lack of a placebo control in this study limits conclusions about the definite efficacy of sertraline and nortriptyline for PPD.

The only other published randomized controlled study compared paroxetine and the combination of paroxetine and CBT in 35 women with comorbid postpartum depression and anxiety disorders.[224] Paroxetine was flexibly dosed over 12 weeks, and CBT was administered in 12 individual weekly sessions. About one-half of the total sample of women were breastfeeding. Both treatments led to significant improvements on the 21-item HAMD (mean scores decreased from 22.1 to 4.5 for paroxetine alone and from 21.1 to 6 for paroxetine with CBT), and there were no significant differences between treatments. The lack of a placebo control in this study, as well as the comorbid anxiety in the subjects, limits conclusions about the efficacy of these treatments for most women with PPD.

There have been some small open trials of antidepressants for PPD. Flexible-dose sertraline was administered for 8 weeks to 26 postpartum women.[225] Baseline 21-item HAMD scores significantly improved from 22 to 7 at end point. Another open trial described the use of flexible-dose venlafaxine for 15 women with PPD.[226] Ten women (67%) completed the 8-week study, and significant improvement was noted from baseline to end point on the HAMD (mean scores decreased from 26.1 to 7) and the CGI-I (mean scores decreased from 4.6 to 1.8). Breastfeeding women were excluded from this study. A case series reported on 6 women with PPD who were treated for 8 weeks with flexible-dose fluvoxamine.[227] Five of the 6 women completed the study, and 4 women (67%) achieved HAMD scores of 7 or less. An 8-week, open, flexible-dose study of bupropion in 8 women with PPD re-

ported median HAMD scores that decreased from 20.5 to 10. Two of the 8 women were breastfeeding, and no adverse effects were noted in their infants.[228] Other small, open reports have suggested efficacy with venlafaxine,[229] phenelzine,[230] fluoxetine,[231] sertraline[232] and TCAs.[233,234] Thus, although antidepressants appear to be effective for PPD, there has not yet been a double-blind, placebo-controlled, randomized trial in women with moderate-to-severe PPD symptoms that includes predominantly breastfeeding women.

Antidepressants and breastfeeding

The American Academy of Pediatrics published breast-feeding rates from a National Immunization Survey conducted in the United States in 2002.[235] Initially, 71.4% of infants were breastfed; at 3 months, 42.5% of infants were exclusively breastfed and 51.5% were partially breastfed; at 6 months, 13.3% of infants were exclusively breastfed and 35.1% were partially breastfed; at 1 year, 16.1% of infants were receiving some breast milk. Some studies have suggested that women with depression may be less likely to initiate or maintain breastfeeding,[236] but the 2002 survey suggests that more than two-thirds of breastfeeding mothers with depression are likely to at least start breastfeeding. Thus the risk–benefit assessment of treatment options for the breastfeeding woman with PPD includes the known risk to the child of not treating maternal depression, the efficacy of antidepressant medication for PPD and the risk of exposing the infant to antidepressant medication.

In contrast to the lack of compelling treatment efficacy data, there are increasing observational reports regarding the transmission of antidepressants in breast milk, mother and infant serum measures and the presence or absence of adverse effects in the nursing infants (Box 2). The presence of antidepressants in an infant's serum is not necessarily harmful in the short or long term. Conversely, an undetectable infant serum level does not mean that the infant is free from antidepressant exposure.[237] Breast-milk analyses and measurements of infant antidepressant serum levels are not routinely obtained in clinical care. Infants should be monitored for possible effects from medication such as irritability, sedation or change in feeding patterns, and increased monitoring for adverse events is necessary in premature or medically ill neonates.[164] Infant exposure to antidepressant medication may be minimized by breastfeeding before daily dosing and by avoiding breastfeeding at the time of peak antidepressant concentration in the breast milk, which varies according to the pharmacokinetics of the antidepressant. A recent case report stated that mirtazapine levels in breast milk peaked 4 hours after the mother took her daily dose,[238] and another study reported that breastfed infants' exposure to sertraline decreased 17.1% when the breast milk was discarded 8–9 hours after maternal sertraline ingestion.[239]

There are several comprehensive reviews of the safety of using TCAs, SSRIs and newer antidepressants while breast-feeding.[11,240–251] A pooled analysis of antidepressant levels in mother–infant dyads concluded that sertraline, paroxetine and nortriptyline usually yield undetectable infant serum

levels and that elevated infant levels are more likely with fluoxetine and citalopram.[249] In addition to the comprehensive reviews cited, the 2 recently published treatment studies in women with PPD add significantly to the absence of reported adverse effects of paroxetine,[224] sertraline[222] and nortriptyline[222] in breastfeeding infants. One study reported that, even though maternal platelet serotonin concentrations decreased with sertraline treatment, infant platelet serotonin transport was not affected, indicating a possible lack of, or minimal effect on, central serotonin transport in the infant.[252] Exposure to sertraline appears to confer minimal risk to breastfeeding infants and is the recommended first-line treatment for PPD in one consensus guideline.[253] Paroxetine has a particularly low milk/plasma ratio, and another consensus guideline recommends it while breastfeeding.[254]

There are mixed reports of adverse effects in breastfeeding infants exposed to fluoxetine. Although several case reports and case series have not identified adverse effects in infants, there have been reports of somnolence, fever and hypotonia,[255] colic and poor sleep,[256] crying, irritability and poor feeding,[257] seizure[258] and a decreased growth rate.[259] Increased infant serum levels of fluoxetine and norfluoxetine have been related to maternal fluoxetine daily doses greater than 20 mg and to exposure during the third trimester of gestation.[260–262] Fluoxetine is generally not considered a first-line medication option for PPD in breastfeeding mothers because there are mixed reports of adverse effects and because of the potential accumulation of fluoxetine and norfluoxetine due to their long half-lives. However, if a woman is already taking fluoxetine, monitoring of the infant for adverse effects may be more advisable than switching antidepressants.[240]

Since the publication of the reviews cited above, there have been recent reports of a lack of adverse effects in breastfeeding

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Box 2: Risks of postpartum depression and psychotropic medications with breastfeeding

Untreated postpartum depression
- Impaired mother–infant attachment
- Cognitive impairment, behavioural dyscontrol, psychiatric disorders in children

Antidepressants
- Sertraline, paroxetine and nortriptyline compatible with breastfeeding
- Adverse effects reported with fluoxetine, citalopram, bupropion, nefazodone and doxepin
- Studies of long-term effects on child development lacking

Antipsychotics
- Limited data

Lithium
- Not recommended owing to high levels in breast milk and adverse effects in infant

Carbamazepine
- Compatible with breastfeeding

Valproate
- Compatible with breastfeeding

Lamotrigine and other antiepileptics
- Limited data

Benzodiazepines
- Sedation and withdrawal possible

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infants from citalopram,[75] escitalopram,[263–265] mirtazapine[238,266] and a fluvoxamine-quetiapine combination.[267] There were earlier reports of poor sleep[268] and irritability or restlessness[269] with citalopram. An infant seizure has been reported with exposure to bupropion.[270] Somnolence, poor feeding and poor temperature regulation have been reported in infants exposed to nefazodone.[271] To date, no reports have been published regarding duloxetine in breastfeeding infants. Doxepin is the only TCA with reported adverse effects found in 2 breastfeeding infants; these included shallow respiration and sedation[272] and poor sucking and swallowing, muscle hypotonia and vomiting.[273] There are very few studies examining long-term cognitive, neurologic and behavioural development in children exposed to antidepressants through breastfeeding.[87]

Other psychotropic medications and breastfeeding

Other psychotropic medications are sometimes used as adjunctive medications for PPD complicated by severe anxiety or for mood stabilization in bipolar or psychotic illness. Benzodiazepines may be used to improve anxiety or insomnia, in particular, before an antidepressant medication takes effect. Sedation and withdrawal symptoms have been reported in breastfeeding infants, and divided low dosages have been suggested.[96,274] Lithium has not been recommended during breastfeeding owing to reports of hypotonia, hypothermia, cyanosis, T-wave inversion and lethargy in infants.[102,110,275,276] However, a recent report suggested that lithium could be safely administered under certain conditions that include the monitoring of infant serum levels.[277] Carbamazepine and valproate have been used safely during breastfeeding, and preliminary data suggest that lamotrigine, oxcarbazepine, topiramate, gabapentin and levetiracetam are not associated with adverse effects even when levels in the breast milk are high.[102,105,110,112,275,276,278]

The published reports of antipsychotic medication use with breastfeeding are increasing, and a recent guideline suggested preference of antipsychotic to antiepileptic medication with breastfeeding.[279] To date, reports of adverse effects are absent with risperidone, with quetiapine alone and with quetiapine combined with fluvoxamine or venlafaxine.[267,280,281] Mild developmental delay was noted in 2 infants treated with a combination of quetiapine and paroxetine; however, the delay did not correlate with medication levels in the breast milk, so underlying disease could have been causative.[280] There have been mixed reports in the case of infants exposed to olanzapine and clozapine,[124,275] and there are no published reports for aripiprazole or ziprasidone. Sporadic adverse effects have been reported with use of traditional antipsychotics.[274] Few studies have examined the long-term effect on child development of exposure to mood stabilizers and antipsychotics during breastfeeding.

Psychotherapy

IPT is a time-limited therapy with demonstrated efficacy for the treatment of MDD; it is designed to relieve depressive

symptoms by assisting patients to make modifications in their interpersonal relationships and by addressing issues such as role change, social support, the marital relationship and life stress.[282] IPT is the most extensively studied psychosocial treatment for PPD. O'Hara and colleagues[136] conducted a large-scale randomized controlled trial in 120 women with PPD. In it, 12 sessions of individual IPT were compared with a wait-list control condition, and IPT was shown to have superior efficacy. IPT significantly improved mean 17-item HAMD scores from 19.4 to 8.3, whereas mean HAMD scores improved from 19.8 to 16.8 in the wait-list control condition. Social adjustment scores also improved with IPT in this sample of women with the full spectrum of PPD severity. Additional support for the use of IPT for PPD includes a study of 35 women with PPD, in which 12 sessions of individual IPT and 12 weeks of a mother–infant therapy group were both significantly superior to a wait-list condition in reducing depressive symptoms.[283] Two small, open studies of IPT administered in group sessions to women with PPD demonstrated significant pre- to posttreatment improvement in HAMD and EPDS scores.[284,285]

The studies of other psychosocial interventions for PPD have been extensively reviewed.[132,218,286–288] Some positive results have been reported with lay peer support, support groups led by nurses or health visitors, individual counselling in the home and group therapy led by mental health professionals.[288] Many of the studies have limitations that include examination of mild PPD only, small samples, lack of a control group and poorly defined treatment interventions. Two studies with sizeable samples compared psychological treatments for women with PPD. One study compared cognitively oriented therapy focusing on mother–infant interaction, psychodynamically oriented therapy, nondirective counselling and routine primary care in 193 women with PPD. It reported that psychodynamically oriented therapy was superior at 4.5 months but that none of the 3 treatments were superior to routine care in the long term.[289,290] Another study reported that group CBT, individual counselling and group counselling were each superior to routine primary care in 192 women with PPD.[291]

Psychotherapy is often preferred to medication for treatment of MDD,[292] particularly in postpartum women who are breastfeeding.[232,293–295] More controlled studies of psychotherapeutic interventions for PPD are needed, as are studies comparing psychotherapy with medication. A meta-analytic review reported that antidepressant medication and antidepressants administered with CBT currently have the largest effect sizes for the treatment of PPD.[132] It has been suggested that women with mild PPD may be sufficiently treated by non–mental health professionals and by individual or group counselling, whereas women with severe PPD may need medication with or without IPT or CBT administered by trained professionals.[288]

Other treatments for PPD

Preliminary reports have suggested that postpartum administration of estrogen may improve mood, but in these studies, a substantial number of the women with PPD were also receiving antidepressant medication.[296,297] As reviewed, there is no evidence suggesting that the postpartum administration of progesterone improves mood.[240] Omega-3 fatty acids are of growing interest owing to studies suggesting their efficacy as adjunctive treatments and as monotherapy for MDD.[298–300] Recent studies have reported a lack of correlation between fish consumption in pregnancy, fatty acid levels and risk of PPD.[301,302] Two studies reported negative results for the prevention of PPD with the administration of omega-3 fatty acids.[303,304] A recent preliminary open trial suggested benefit of omega-3 supplementation for PPD.[305] In addition, there are positive reports regarding herbs,[306] light therapy,[307] sleep deprivation,[308] massage,[309,310] infant sleep intervention[311] and exercise.[312–314]

Treatment dilemmas for postpartum women with MDD

The postpartum woman with a psychiatric disorder who is breastfeeding faces a treatment dilemma. The negative effects of untreated PPD on short-term and long-term child development are well established. Women with PPD may seek psychotherapy as a first treatment, but psychotherapy will not always be effective, and women with severe symptoms may need to consider antidepressant medication. Barriers to psychotherapy as an optimal treatment choice include limited availability of therapists highly trained in IPT or CBT, time commitment, child care issues, cost and the sensitivity of the therapist to cultural and sociodemographic factors.[137,240] Women who breastfeed need to be aware that all psychotropic medications pass into breast milk and that the potential for infant exposure exists with each medication. Although many observational reports suggest that many psychotropic medications lack adverse effects in infants, few studies have examined long-term neurocognitive or neurobehavioural effects. Discussions of the treatment options with the postpartum patient and her partner need to include the risks of no treatment, available data about the safety of medications while breastfeeding, the patient's personal psychiatric history and previous treatment responses, her individual treatment preferences and her expectations.[148] Once a medication is selected, low initial dosages and slow titration are advised, with monitoring of the infant for adverse effects.[240] Collaboration with the pediatrician is important. If adverse effects in the infant are noted, options include decreasing the dose, changing to partial breastfeeding or changing the medication.

Conclusion

The screening and identification of pregnant and postpartum women with psychiatric disorders needs much improvement. When mental health disorders have been identified, there are many barriers to accessible, acceptable and effective treatment. Women with depression who are pregnant or postpartum and breastfeeding face difficult treatment decisions. Untreated stress, anxiety and depression, as well as psychotropic medications, all involve exposure to the fetus and child. Each month, new studies of the effects of untreated disease and medications on the fetus and breastfeed-

ing infant are published. The clinician can remain informed by monitoring these studies and reviews, as well as by monitoring websites that update information frequently for both the clinician and the patient, such as www.motherrisk.org and www.womensmentalhealth.org. Future studies are needed to confirm the efficacy of antidepressants in perinatal depression, compare antidepressants with psychotherapy and compare combined psychotherapy and antidepressant treatment with either treatment alone. Factors governing a patient's choice of treatment need to be futher identified. There is a definite need for systematic longitudinal studies examining the effects of medication exposure as well as exposure to untreated disease on child neurologic and behavioural development.

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