2 Prevalence, Clinical Course, and Management of Depression During Pregnancy

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Summary

Depression has been identified by the World Health Organization as a major cause of morbidity in the 21st century. As women between 25 and 44 yr represent the population at highest risk for depression, a substantial number are likely to become pregnant while suffering from this illness. In this chapter, we summarize the prevalence and clinical course of depression during pregnancy. We also document evidence-based information regarding the safety and efficacy of both pharmacological and nonpharmacological treatments of prenatal depression. In addition, we discuss other issues surrounding the treatment of depression, such as abrupt discontinuation syndrome, poor neonatal adaptability, and an increase in the rate of spontaneous abortions, associated with the use of certain antidepressant drugs. Of equal importance, we also review the emerging literature on the potential adverse effects of untreated depression during pregnancy.

Depression is an important issue that must be addressed when women become pregnant. A variety of pharmacological and nonpharmacological treatment options are available, the vast majority of which appear to be relatively safe. Women suffering from depression during pregnancy must be treated individually, and the benefits and/or risks of treatment or nontreatment should be weighed carefully using evidence-based information. This approach will ensure the best possible outcomes for the mothers and their babies.

Key Words: Depression; pregnancy; risks; prevalence; course; treatment; safety.

1. INTRODUCTION

Depression has been identified by the World Health Organization as a major cause of morbidity in the 21st century *(1)*. The Global Burden

From: *Current Clinical Practice: Psychiatric Disorders in Pregnancy and the Postpartum: Principles and Treatment*
Edited by: V. Hendrick

of Disease study *(2)* states that major depression will become the second leading worldwide cause of disease burden by 2020. In the United States alone, the prevalence of depression has been estimated by the National Institutes of Health at between 5 *(3)* and 10.3% *(4)*.

Major depressive disorder (MDD) is threefold more common in women than in men *(5)*. Furthermore, the prevalence of depression is highest in women between the ages of 25 and 44 *(6)*. Therefore, a large group of women are likely to experience depression during their childbearing years. Recent studies document the incidence of depression during pregnancy in about 30% of all patients in the United States *(7)*. Women who have been depressed prior to pregnancy appear to be at an elevated risk for depressive episodes during subsequent pregnancies *(8)*.

2. PREVALENCE

Studies focusing on the prevalence of depression during pregnancy have recently increased, with 21 studies published in the last 9 yr in contrast to only 9 studies published between 1985 and 1995 *(9)*.

2.1. Current Prevalence Data

Although wide variations exist in estimates of the prevalence of depression in pregnancy *(10,11)*, recent evidence suggests that the prevalence of depression during the first trimester of pregnancy is approx 7.4% *(12)*. During the second trimester, prevalence of the disease rises to 12.8%, and remains virtually unchanged at 12% in the third trimester *(12)*. It is critical to note, however, that many women choose not to participate in prenatal care until well into the second trimester. Therefore, the low prevalence of depression observed during the first trimester may simply be the result of depressed women not seeking prenatal care during that period *(12)*. Also of note is the fact that postpartum depression in some patients is known to begin prenatally and increase dramatically in severity during the postpartum period *(1)*.

2.2. Tools Used to Detect the Presence of Depressive Symptoms in Pregnancy

Much of the recent epidemiological data on depression has been obtained via the use of lay-administered self-report questionnaires, some of which have been validated for use in pregnant women. The items contained in the questionnaires are based on those contained in previously validated instruments and the diagnostic criteria for MDD set forth by the fourth edition of the *Diagnostic and Statistical Manual*

of Mental Disorders (DSM-IV) *(13)*. These lay-administered tools facilitate data collection from a variety of patient groups. Furthermore, they reveal the presence of depressive symptoms without the need for time-consuming, costly analyses by mental health professionals. Specific details regarding four of the most commonly used self-report inventories are outlined here.

2.2.1. Beck Depression Inventory

The Beck Depression Inventory (BDI), first introduced in 1961, was revised and re-released in 1978 as a brief 10-min, self-administered questionnaire capable of detecting the presence of depressive symptoms in both female and male psychiatric patients. The BDI consists of 21 questions regarding various aspects of mood, including but not limited to sadness, suicidal ideation, loss of weight, and social withdrawal *(14,14a)*. The BDI has been validated for use in pregnant women via comparison against the National Institute of Mental Health Diagnostic Interview Schedule III *(15)*. It should be noted, however, that responses to items on the BDI referring to physical disturbances (loss of sleep, fatigability) are often positive in nondepressed obstetric patients because of the changing physical demands of pregnancy. This fact should be kept in mind when using the BDI to assess the severity of depression in these patients *(12,16)*. The cutoff score denoting the presence of depressive symptoms is 16 or more.

2.2.2. Edinburgh Postnatal Depression Scale

The Edinburgh Postnatal Depression Scale (EPDS), first published in the *British Journal of Psychiatry* in 1987 *(16)*, is also validated for use in pregnant populations *(17)*. This 10-question inventory specifies that it should not be used as a diagnostic tool, and all results should be confirmed by a careful clinical assessment. Women who score above the cutoff of 12 are likely to be suffering from a depressive illness. The EPDS has a sensitivity of 0.50 and a specificity of 0.90 for the detection of depressive symptoms during pregnancy *(18)*. It detects only mood-related signs of depressive symptoms in order to avoid false-positives owing to erroneous detection of physiological symptoms consistent with depression as well as normal pregnancy *(12)*.

2.2.3. Primary Care Evaluation of Mental Disorders Patient Health Questionnaire

Validated in 3000 obstetric patients via comparison with telephone-psychologist assessments, the Primary Care Evaluation of Mental Disorders Patient Health Questionnaire (PRIME-MD, PHQ) is considered

an accurate instrument for the detection of recent psychosocial stressors and functional impairment due to mood disorders in pregnant populations *(19)*. The original PRIME-MD was a clinician-administered inventory but was adapted to a patient self-administered questionnaire, with a sensitivity of 0.70 and a specificity of 0.95 *(20)*. Scores of 5–9 are indicative of mild depression, 10–14 of moderate depression requiring psychotherapeutic intervention, and 15 or higher of severe depression requiring immediate pharmacotherapy and likely hospitalization *(21)*.

2.2.4. Center for Epidemiological Study Depression Scale

The Center for Epidemiological Study Depression Scale (CES-D), developed by the National Institutes of Health in 1970, has been used extensively in psychiatric research *(22)*. Although not yet validated for use in pregnant populations, the CES-D is one of the most common instruments used by first-line clinicians and researchers to detect the presence and prevalence of depressive symptoms, both in the general population and in pregnancy. In the general population it has a sensitivity of 1.0 and a specificity of 0.88 for the detection of major depression (1 mo prevalence) when using the cutoff score of 16 or higher to denote the presence of depressive symptoms *(23)*.

2.2.5. Variability in Study Data

It should be noted that studies have been conducted in patients at varying stages of pregnancy. Such variation exists both within and between many of the studies recently conducted on the epidemiology of depression during gestation. Moreover, the type and severity of depressive symptoms between and even within relapse episodes can change. Such changes in symptomatology may have an impact on the accuracy of the results obtained from these studies.

Additionally, one must note the effect of socioeconomic status (SES) on the prevalence of depression and the responses to the self-report questionnaires used in these studies. A negative correlation has been shown between the prevalence of depression and SES *(24,25)*.

3. CLINICAL COURSE

MDD is a highly complex disorder with a variable clinical course. The clinical presentation of the disorder is characterized by one or more major depressive episodes (MDEs), defined by the DSM-IV as 2 or more weeks of depressed mood, anhedonia, and/or loss of interest with any five of the following symptoms: difficulties in concentration, fatigue, feelings of worthlessness or guilt, insomnia or hypersomnia, thoughts of

death, suicidal ideation, weight change, and psychomotor difficulties (agitation or retardation) *(13)*. It is important to note, however, that many of the somatic symptoms cited by the DSM-IV as integral to the diagnosis of depression are also highly common during pregnancy, especially insomnia, weight change, and fatigue. A clinical assessment for depression in any obstetric patient should therefore focus more on the cognitive aspects of depression (feelings of guilt, worthlessness; anhedonia) rather than the physical symptoms.

3.1. Risk Factors

Numerous risk factors have been identified for prenatal depression. Those most commonly observed are previous depressive illness, lack of social support, negative life events in the preceding pregnancy *(26)*, negative attitudes toward pregnancy, unplanned or first pregnancy, physical discomfort (e.g., nausea), and previous stillbirth *(27,28)*. Additionally, poor prenatal care, poor marriage dynamics, remarriage, and substance abuse/dependency have also been identified as risk factors for depression in pregnancy *(29–31)*.

The single most significant predictor of postpartum depression (PPD) is prenatal depression *(32–35)*. A meta-analysis by Beck and colleagues *(33,36)* revealed a comprehensive list of predictors of PPD, including prenatal depression, child-care stress, life stress, lack of social support, prenatal anxiety, maternal relationship dissatisfaction (e.g., marital problems), history of previous depression, difficult or unpredictable infant temperament, maternity blues (tearfulness, anxiety, irritability, and labile mood in the first 10 d postdelivery) *(37)*, low self-esteem, and low SES *(33,38)*. PPD begins during the later stages of pregnancy in 25% of patients *(39)*.

As mentioned earlier, peak prevalence of depression in females occurs during the childbearing years, between ages 25 and 44 *(6)*. An apparent clustering of depression occurs between ages 20 and 30 *(9,40,41)*. MDD in obstetric patients is characterized by one or more MDEs (6–12 mo in length if left untreated) *(9,40)*.

Fifty percent of patients treated for MDD experience full remission of their symptoms *(42)*. However, 85% of recovered patients relapse to a subsequent MDE within 15 yr of treatment *(42)*, and a large proportion of these patients remain chronically depressed *(43,44)*.

Symptoms of prenatal depression, which can occur at any time during pregnancy, can vary in intensity, duration, and type. To date, however, there has not been a clearly established pattern of symptom progression or change in antenatal depression *(45)* because investigations on the

topic have yielded conflicting results. One study that examined mood in a group of depressed pregnant patients during the first trimester noted improvements in mood over the second and third trimesters of pregnancy *(46)*, whereas the results of a second prospective study showed depressive symptoms to be at their height in the third trimester (34–38 wk) *(47)*. Further study in this area is ongoing.

4. RISKS OF UNTREATED DEPRESSION DURING PREGNANCY

Many pregnant, depressed women experience an amplification of physical symptoms during pregnancy, including increased heart rate, loss of appetite, stomach pain, headaches, and sexual dysfunction *(48)*, during both the period leading up to and during MDEs. However, the risks of untreated depression go well beyond the somatic symptoms cited previously. Past studies suggest that the most notable adverse pregnancy outcomes associated with antenatal depression include increases in spontaneous preterm delivery *(49,50)*, low birthweight (LBW), and small-for-gestational age infants *(9)*. There are, however, a number of intermediate risks associated with inadequate treatment of depression during pregnancy, all of which are also associated with both short- and long-term deleterious maternal and neonatal health effects *(9)*. These risks are summarized below.

4.1. Functional Impairment

Recent research suggests that women who are either depressed or are experiencing severe anxiety during the first trimester of their pregnancies exhibit some degree of functional impairment *(51)*. This impairment may take the form of reduced work productivity, continuous and/or prolonged absence from work *(52)*, and increased health care utilization *(53)*. In cases where the depressed woman is the only working member of a family, such an impairment could also have negative consequences on her family; her family's financial status, for example, would likely decline.

4.2. Substandard Maternal Nutrition and Increased Maternal Weight Loss

As loss of appetite is often associated with depression, untreated depression during pregnancy may result in substandard maternal nutrition and lower-than-normal maternal weight gain. Studies have shown that intrauterine growth retardation (IUGR) and low neonatal birthweights have been linked to inadequate maternal nutrition and/or low maternal

weight gain *(54)*. The Centers for Disease Control have classified LBW as the second leading cause of neonatal morbidity and mortality *(55)*.

4.3. Substance Abuse

Although a causal relationship between depression and substance abuse has not been clearly elucidated, the connection between depression and substance abuse (especially smoking and alcohol use) is of note. Depression during pregnancy is significantly associated with prenatal substance abuse. Finnish studies have found substance abuse to be co-morbid with depression in 6.4% of women *(56)*. Also, in a recent US study of 186 pregnant women, 8% were found to have both psychiatric illnesses and substance abuse disorders *(57)*. More critically, a study of 1014 women of low SES showed depressive symptoms (as per CES-D scores ≥16) to be significantly associated with smoking, as well as alcohol and cocaine use *(57a)*. Alcohol consumption, smoking, and street drug use have been clearly associated with neonatal morbidity and mortality when used or consumed in even small to moderate amounts during pregnancy *(9)*.

4.4. Pregnancy-Induced Hypertension

Pregnancy-induced hypertension (PIH) is considered a serious complication during pregnancy *(9)*, and pre-eclampsia, a form of PIH, has been associated with depression during pregnancy *(58)*. Some of the symptoms associated with severe pre-eclampsia are hypertension, proteinuria, with associated edema in the last half of pregnancy, headaches, visual disturbances, and upper abdominal pain *(9,59,60)*. Although the etiology of this condition is as yet uncharacterized, investigators have hypothesized that altered elimination of vasoactive hormones as a result of depression may increase the risk for PIH *(58,61)*. A recent Finnish study found a 2.5-fold increase in the risk of pre-eclampsia in pregnant women suffering from depression *(61)*.

4.5. Inadequate Prenatal Care

The lack of motivation and self-esteem associated with depression during pregnancy may lead to inadequate prenatal care because depressed women are known not to seek out prenatal care until well into their pregnancies *(62)*. Previous studies have found that women with psychiatric disorders attend fewer than 50% of prenatal care appointments *(62)*. A cohort study of almost 10.6 million births found a relative risk (RR) of 2.8 for preterm birth in Caucasian women with inadequate prenatal care compared to women with prenatal care throughout their pregnancies *(63)*. Additionally, these researchers additionally found an

RR of 3.3 for fetal death and an RR of 1.7 for postnatal death in women lacking prenatal care throughout their pregnancies *(64,65)*. Upon adjustment for the presence of various maternal high-risk conditions, the RRs for fetal and postnatal deaths remained elevated at 4.3 and 1.6, respectively, in women without any high-risk conditions and without prenatal care *(64,65)*. Furthermore, the study identified a negative relationship between the number of prenatal care visits and the risks for both fetal and postnatal deaths. These findings clearly underscore the potential dangers of inadequate prenatal care.

4.6. Postpartum Depression

Perhaps one of the most notable consequences of untreated antenatal depression is the subsequent increase in risk for PPD. Although a number of recent studies have examined the incidence of PPD in women with antenatal depression, the most notable evidence comes from studies using Beck's Postpartum Depression Predictors Inventory (BPDPI) *(38)*. A recent meta-analysis of 26 studies using BPDPI showed prenatal depression to be an extremely strong predictor of PPD *(33)*.

4.7. Poor Neonatal Behavioral Development

Recent investigations have shown that infants born to depressed mothers tend to exhibit excessive crying, lower orientation scores, inferior excitability, and few expressions of interest shortly after birth, indicating the possibility of neurodevelopmental consequences of maternal depression in the newborn *(66,67)*.

Altered levels of cortisol, norepinephrine, and dopamine have been detected in babies of depressed mothers *(9)*. Moreover, in depressed pregnant women, levels of cortisol and norepinephrine have been elevated and levels of dopamine have been reduced during the third trimester of pregnancy. Furthermore, these altered levels have been found to significantly predict similar alternations in the levels of these substances in neonates *(67)*. These findings lend support to the hypothesis that biological imbalances associated with depression in the mother may affect fetal mood development and hormone distribution, especially given that cortisol, dopamine, and norepinephrine are known to cross the placenta (to varying degrees) *(68)*. Mother–baby interactions are also known to suffer in women with depressed mood *(69)*.

5. TREATMENT OF DEPRESSION DURING PREGNANCY

A number of options for the treatment of depression during pregnancy are available. Interpersonal psychotherapy (IPT) has been shown to be

effective in the treatment of women diagnosed with prenatal depression *(9)*. Studies have also noted the efficacy of electroconvulsive therapy (ECT) in the treatment of severely depressed and suicidal pregnant patients *(70,71)*. Most notably, an increase in the use of pharmacotherapy for the treatment of depression during pregnancy has been noted in several studies *(72)*.

The selection of a treatment modality for depression in pregnant patients is generally a function of the severity of the disorder and its associated symptoms. The clinical management of depression during pregnancy should occur on a case-by-case basis. The decision-making process should center on informed decision making by the patient, with the assistance of her health care provider *(73)*.

5.1. Nonpharmacological Treatment Options

5.1.1. Interpersonal Psychotherapy

Two major studies involving the use of IPT for pregnant, depressed women were undertaken by the same investigator *(74,75)*. Both investigations found IPT to be an effective therapy for antepartum depression *(74,75)*. It should be noted, however, that no investigations have compared IPT to antidepressant treatment. Although data on the efficacy of IPT for prenatal depression are not as extensive as those for antidepressants, it is a reasonable treatment option for patients who wish to avoid the use of medications or who experience antidepressant-refractory illness.

5.1.2. Electroconvulsive Therapy

Data from several investigations now exist that attest to the safety of ECT in pregnancy. Recent reviews on the subject *(70,71)* suggest that ECT is both safe and efficacious for the treatment of severe and/or antidepressant-refractory forms of MDD. A recent review cites 300 case reports regarding the use of ECT in pregnancy over the past half century. Among the cited reports, only four cases of premature labor were described, and premature membrane rupture did not occur in any case *(76)*. Given the reports of its relative safety and efficacy, some clinicians may wish to consider ECT as an alternative to antidepressant therapy *(76)*.

5.2. Pharmacological Treatment Options

The baseline incidence of congenital malformations in the general population is approx 1–3% *(77–79)*. The greatest potential for drug-related physical teratogenesis occurs in the first 12 wk of pregnancy, because the majority of organogenesis occurs within this period. It should be noted, however, that studies are required in all trimesters to clearly

establish a given drug's safety in pregnant patients. A summary of the safety of the pharmacological treatments discussed here can be found in Table 1.

5.2.1. Tricyclic Antidepressants and Safety in Pregnancy

Imipramine, the first of the tricyclic antidepressants (TCAs), was introduced in 1958 *(80)*. Since then, more than 10 other TCAs have been designed, produced, and marketed. These agents achieve their antidepressant effects principally via inhibition of central norepinephrine reuptake and, to a lesser extent, serotonin reuptake *(80)*. Although TCAs have been widely prescribed, their use has declined over the past 20 yr, likely due to the advent of medications with fewer adverse effects. In the early 1970s, a case report of a child born with bilateral amelia following *in utero* TCA exposure *(81)* caused widespread fear that TCAs were teratogenic. Since then, 3 prospective and more than 10 retrospective studies have become available regarding the safety of TCA use in the first trimester of pregnancy *(82–88)*. The individual and pooled results of these studies suggest that TCA use in pregnancy is not associated with an increase in the risk of congenital malformations above the baseline.

It should be noted that transient withdrawal symptoms have been noted following TCA exposure in late gestation, including irritability, rapid breathing, and urinary retention *(89)*.

5.2.2. Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRI) antidepressants, although relatively new, are the most widely prescribed antidepressants in the world today *(90)*. The advent of these agents highlighted the role that serotonin or 5-hydroxytryptamine plays in the pathophysiology of mental illness.

SSRIs show remarkable selectivity for the serotonergic system over the noradrenergic or cholinergic systems and, as such, have much wider therapeutic windows and more favorable tolerability profiles compared with earlier antidepressant medications *(91,92)*.

5.2.2.1. Fluoxetine (Prozac). Of all the SSRIs currently prescribed in pregnancy, fluoxetine is the best studied. Fluoxetine has been demonstrated to cross the placenta in both animal *(93)* and human studies *(94,95)*. Fluoxetine was shown to cross the placenta in larger amounts than all other SSRIs, with the exception of citalopram *(95)*.

Five recent prospective studies *(83,96–98a)* and four retrospective studies have examined the safety of fluoxetine use in pregnancy *(82,99–101)*. In these nine studies, more than 1700 pregnancies exposed to fluoxetine at vary-

Table 1
Summary of Antidepressants in Pregnancy

Class	*Drugs studied*	*Safety in pregnancy*
Tricyclic antidepressants	Clomipramine, amitriptyline, imipramine, doxepin, dothiepin, trimipramine, nortriptyline, lofepramine, desipramine, maprotiline, protriptyline	As a group, considered relatively safe to use in pregnancy; however, associated with maternal toxicities and neonatal withdrawal
Selective serotonin reuptake inhibitors	Fluoxetine, paroxetine, citalopram, sertraline, fluvoxamine	All except fluvoxamine are well studied and considered relatively safe for use in pregnancy; however, have been associated with perinatal complications including jitteriness, respiratory distress, hypoglycemia
Monoamine oxidase inhibitors	Tranylcypromine, phenelzine; no others studied	Not recommended for use in pregnancy because of paucity of data and possible toxicities
Others	Venlafaxine, bupropion, trazodone, nefazodone, mirtazapine, St. John's wort (SJW)	Based on one prospective comparative study on each drug, venlafaxine bupropion, trazodone, and nefazodone appear to be relatively safe in pregnancy; data on mirtazapine and SJW limited

ing stages (1418 prospectively, 289 retrospectively) were examined. None of these studies showed an increase in the rate of major malformations—physical deformities that are life-threatening, require major surgery, or are associated with serious cosmetic or functional effects *(102)* —above the 1–3% baseline risk that exists in the general population. Moreover, all but two of these studies *(83,97)* showed no statistically significant increases in the risk for spontaneous abortion, LBW or major neonatal health complications following exposure to fluoxetine in early

or late pregnancy or throughout gestation *(82,83,96–101)*. It should be noted that the vast majority of the 1280 prospectively followed pregnancies were compared with matched controls, and no differences in the rates of major malformations between the two groups were seen.

Chambers and colleagues prospectively examined 228 pregnant women taking fluoxetine throughout gestation and compared their outcomes with those of 254 prospectively identified comparator women exposed to known nonteratogens. In this investigation, the incidence of major malformations in the fluoxetine-exposed group (5.5%) was no different from that observed in the nonteratogen-exposed comparator group (4%) The rate of spontaneous abortions also did not differ significantly between the fluoxetine exposed and comparator groups (10.5 vs 9.1%, respectively). This study did, however, find a significant increase in the rate of three or more minor anomalies, LBW and length, preterm delivery, and admission to special care nurseries in infants whose mothers were exposed to fluoxetine in the third trimester *(97)*. The study also observed an increase in poor neonatal adaptation, characterized by transitory jitteriness, respiratory difficulty, and cyanosis upon feeding in infants exposed to fluoxetine in late gestation (*see* Section 5.3.1. for a brief discussion of poor neonatal adaptation). Confidence in the results obtained from this study *(97)* is limited by several methodological issues, including a lack of control for the effects of the underlying depressive illness. Additionally, maternal age in the fluoxetine-exposed group was higher than in the control group, a factor known to affect birthweight *(103)*. Furthermore, a large proportion of the women in the fluoxetine-exposed group were also exposed to nicotine and other psychoactive medications.

In a study by Pastuszak et al. *(83)*, 128 gravid women taking a mean daily dose of 25.8 mg of fluoxetine during the first trimester were followed and compared with two matched control groups (each of 74 patients) exposed to either TCAs or known nonteratogens. The investigators found no differences in the rates of major malformations between any of the comparison groups, but they did find a slightly increased risk of spontaneous abortions in the fluoxetine- and TCA-exposed groups (13.5 and 12.2%, respectively) vs the nonteratogen comparator group (6.8%). These increases, however, did not reach statistical significance. Moreover, as is the case in the study by Chambers et al. *(97)*, it is unclear whether the higher incidence of spontaneous abortions observed in both the fluoxetine- and TCA-exposed groups was the result of the effects of the medications, the underlying maternal depression, or other factors.

Another prospective study by Hendrick et al. found an increase in LBW in the infants of mothers exposed to high-dose fluoxetine (40–80 mg/d)

throughout gestation, despite comparable maternal weight gain across all experimental groups *(98a)*. Women exposed to nicotine, alcohol, or recreational drugs were excluded, thereby removing these as potential confounding factors. It should be noted, however, that this study had no matched comparator group.

A significant concern associated with psychoactive medication use during pregnancy is the potential for long-term neurodevelopmental abnormalities, including cognitive and language impairment and behavioral teratogenesis. A study by Nulman et al. assessed global IQ, language development, temperament, mood, arousability, activity-level distractibility, and behavior in the children of 80 mothers exposed to TCAs and 55 mothers exposed to fluoxetine during pregnancy *(104)*. Assessment of IQ and language development occurred between 16 and 86 mo of postnatal age. These investigators found no differences in any parameter examined between the TCA-exposed, fluoxetine-exposed, and non-antidepressant-exposed groups.

5.2.2.2. Paroxetine (Paxil). The use of paroxetine during pregnancy has also been the subject of recent study. Paroxetine has been shown to cross the placenta in detectable amounts in a recent human placental kinetics study *(95)*.

Currently, data on paroxetine use in pregnancy are somewhat limited. To date, published data on 305 exposures to paroxetine at varying stages in pregnancy (274 prospectively followed and 31 retrospectively evaluated) *(82,99,101,105,106)* are available. None of these studies has shown an increase in the risk of major malformations compared with the general population or a matched comparator group *(105,106)*. Additionally, these studies have found no evidence linking paroxetine use at any time in pregnancy to an increase in spontaneous abortions or other major neonatal health complications. One of these studies did report evidence of poor neonatal adaptation in infants whose mothers used paroxetine in the third trimester *(106)*.

Recently, an unpublished retrospective, cohort study (supplemented by a nested case–control study) examined the effects of antenatal exposure to various antidepressants, including paroxetine (studied only via *post hoc*, secondary analyses) on pregnancy outcome. This study, conducted by GlaxoSmithKlein (GSK) utilized medical records taken from two large medical databases, containing medication (and pharmacy dispensing) records from more than 25 health insurance providers *(106a)*. The results of *post hoc* analyses from this study showed an adjusted odds ratio of 1.84 (95% CI 1.16–2.91) for congenital malformations associated with paroxetine exposure during the first trimester. The adjusted

odds ratio increased to 2.20 (95% CI 1.34–3.63) following the exclusion of data from women exposed to other antidepressants or known teratogens during the study period. The results of this investigation suggested an overall risk of 4% for the development of major malformations following paroxetine exposure in the first trimester (an increase of 1% over the baseline risk) *(106b)*.

The adjusted odds ratio for cardiovascular defects following first-trimester exposure to paroxetine was found to be 2.26 (95% CI 1.17–4.33). The odds ratio diminished to 2.08 (95% CI 1.03–4.23) following the exclusion of data from women exposed to other antidepressants and/or known cardiovascular teratogens during the study period. These data represent an overall risk of 2% for cardiovascular defects (a twofold increase over the 1% baseline risk for cardiovascular defects in the general population) associated with first-trimester paroxetine exposure *(106a,106b)*. The results of this study have recently prompted the US Food and Drug Administration (FDA) to label paroxetine as a "Category D" (demonstrated risk to the fetus) drug.

Although the data from this large epidemiological study are among the first that suggest teratogenicity following paroxetine use during pregnancy, confidence in the results obtained is limited by several methodological issues. Briefly, both the retrospective nature of the study design and the use of *post hoc* analyses to obtain the adjusted odds ratios for cardiovascular malformations and congenital malformations decrease the grade of evidence ascribable to the results obtained. The lack of a matched control group and the limited medical/clinical data (including information on disease severity) available from the insurance databases used further limits the interpretation of the results obtained *(106c)*. Finally, and perhaps most troublingly, much of the data used in the GSK study was based on pharmacy dispensing records for the various antidepressants studies and thus, did not provided any information on how many of the patients prescribed paroxetine actually consumed their medications regularly and at the doses prescribed (i.e., the degree of paroxetine exposure).

Overall, the data available regarding paroxetine use during pregnancy are conflicting. Although the results of the unpublished GSK study just cited do suggest some degree of caution regarding antenatal paroxetine use, the overall risks of general and/or cardiac malformations in children whose mothers were exposed to paroxetine during the first trimester are only modestly above the risks for these negative pregnancy outcomes in the general population. In general, the available data regarding antenatal paroxetine safety, the potential health risks of untreated depression during pregnancy, and individual patient responsiveness to paroxetine

should all be carefully considered when making decisions regarding the commencement, modification and particularly the cessation of paroxetine use during pregnancy.

5.2.2.3. Citalopram (Celexa, Lexapro). Limited data are available on the use of citalopram during pregnancy. Citalopram has been shown to cross the human placenta in detectable amounts and to a greater degree than all other SSRI antidepressants *(95)*, with the exception of fluvoxamine, whose placental kinetics have yet to be clearly established.

Ericson et al. recently reported the outcome of 375 prospectively followed exposures to citalopram in early pregnancy, of which 364 were exposures to citalopram alone with the remainder being exposures to citalopram in combination with another SSRI or TCA antidepressant *(99)*. The investigators found no statistically significant increases in the incidence of major malformations compared to that expected in the general population. An association between the use of citalopram (and other SSRIs) early in pregnancy and an increase in preterm delivery was noted. This increase, however, was thought by the investigators to be a consequence of the underlying maternal disease.

A second prospective, comparison study followed 11 mothers exposed to citalopram throughout gestation. Pregnancy outcome as well as neurodevelopment was evaluated up to 1 yr of age. No major or minor malformations were detected as part of this study. Additionally, all infants were neurodevelopmentally normal at 1 yr of age *(107)*.

Most recently, The Motherisk Program prospectively followed 106 women exposed to citalopram during their pregnancies (98 in first trimester and 48 throughout gestation) *(107a)*. Their preliminary results documented 92 (86.6%) live births, 11 (10.3%) spontaneous abortions, 2 (1.9%) therapeutic abortions, 1 (0.9%) stillbirth, and 3 (3.2%) major malformations in the citalopram-exposed group. Upon comparison with two matched comparator groups, each consisting of 106 women exposed to other antidepressants or known nonteratogens (respectively), no statistically significant differences in the rates of major malformations, spontaneous abortions, elective terminations, or stillbirths were found between any of the comparison groups.

At present the pregnancy data are on citalopram and not on its isomer, *S*-citalopram (Lexapro).

5.2.2.4. Sertraline (Zoloft). Sertraline has been shown to cross the human placenta in significantly smaller amounts than other SSRI antidepressants *(95,107b)*.

Published literature on 213 pregnancies exposed to sertraline (181 prospectively followed and 32 retrospectively evaluated) is available. A

prospective controlled cohort study by The Motherisk Program *(105)* followed 147 women exposed to sertraline in the first trimester of pregnancy. Of the women exposed, 127 (86%) gave birth to live infants, 12 (9%) experienced spontaneous abortions, and 7 (5%) chose to undergo therapeutic abortions. Among the 127 live births, 4 (3.2%) malformations were observed. There were no statistically significant differences among the observed rates of spontaneous abortions, elective abortions, major malformations, or stillbirths between the SSRI-exposed and matched comparator groups *(105)*.

A second study prospectively followed 32 pregnancies exposed only to sertraline in early pregnancy and 2 other pregnancies exposed to sertraline and other SSRI agents at similar stages of gestation. The rate of major malformations seen in infants of sertraline-exposed women was not statistically different than that observed in the general population *(99)*.

5.2.2.5. Fluvoxamine (Luvox). Very limited data are available regarding the use of fluvoxamine in pregnancy. In a multicenter, prospective, cohort-comparator study by The Motherisk Program *(105)*, 26 women exposed to fluvoxamine in the first trimester of pregnancy were followed. Of the 26 women exposed, 22 (88%) gave birth to live infants. Two of the remaining four women had spontaneous abortions, and two women therapeutically aborted their pregnancies. In the group of live births, three (12%) major malformations were observed. Given the small sample size of this study, these data are not definitive regarding fluvoxamine use in pregnancy.

Additionally, 66 women who took fluvoxamine early in their pregnancies were retrospectively examined by the European Network of Teratology Information Services. This group observed 49 live births with 1 malformation among them, 9 therapeutic abortions (of which 1 was of a malformed fetus), 6 spontaneous abortions, and 2 stillbirths. Although no control group was available for comparison in this study, the rates of live births, spontaneous abortions, and malformations was similar to that expected in the general population.

5.2.3. Other Antidepressants

5.2.3.1. Venlafaxine (Effexor). Venlafaxine, a phenethylamine bicyclic derivative, is chemically unrelated to all other antidepressants *(108)*. Venlafaxine achieves its therapeutic effects via inhibition of both serotonin and norepinephrine reuptake. It has no significant affinity for central acetylcholine or histamine receptors—hence its mild adverse effects profile *(109)*.

To date, only one study evaluating the safety of venlafaxine use in pregnancy exists. In this multicenter study from Motherisk *(108)*, 150 women exposed to venlafaxine in the first trimester of pregnancy (35 of whom took the drug throughout pregnancy) were followed. Of the 150 women, 125 gave birth to live infants, 18 had spontaneous abortions, and 7 had therapeutic abortions. Two major malformations were observed among the 125 live births. The outcomes of these pregnancies were compared to those of two matched-comparator groups, each consisting of 150 women, exposed exclusively to SSRI antidepressants or nonteratogens, respectively. No statistically significant differences in the rates of major malformations, therapeutic abortions, mean gestational ages, or mean birthweights were observed between the exposed and comparator groups. It should be noted that the incidence of spontaneous abortions in the venlafaxine- and antidepressant-exposed groups (12 and 10.7%, respectively) was higher than that in the nonteratogenic comparator group (7.3%). This difference between the groups, however, was not statistically significant.

5.2.3.2. Bupropion (Wellbutrin). Bupropion, an amino ketone compound, is marketed both as an antidepressant and as an aid for smoking cessation. The antidepressant mechanism of bupropion is presently not well understood but is thought to involve both central noradrenergic and dopaminergic pathways *(110)*. Data on the outcomes of 226 pregnancies exposed to bupropion are available from the manufacturer. The outcomes of these pregnancies suggest no increase in the rate of major malformations resulting from exposure to bupropion during pregnancy *(111)*. Recently, a study completed by The Motherisk Program followed 136 women exposed to bupropion in the first trimester or throughout gestation and compared their pregnancy outcomes to those of two comparator groups exposed to other antidepressants (57 women) or known nonteratogens (126 women). Among the 136 exposed pregnancies, there were 105 live births, 20 spontaneous abortions, 10 therapeutic abortions, 1 stillbirth, 1 neonatal death, and no malformations observed. Upon comparison with the matched control groups, no statistically significant differences in the rates of major malformations, stillbirths, neonatal deaths, or major neonatal health complications were detected *(112)*.

This study examined the safety of bupropion during pregnancy in women using it as an antidepressant and/or as smoking-cessation aid. Upon comparison of the pregnancies exposed to bupropion for either indication with matched nonteratogen-exposed comparators, the incidence of spontaneous abortions was significantly higher in the bupropion-exposed group (14.7%) than in the control group (4.5%) ($p < 0.009$) *(112)*.

Interestingly, however, when the incidence of spontaneous abortions in women using bupropion as an antidepressant only (15.4%) was compared with that of women using other antidepressants and nonteratogens (12.3 and 6.7%, respectively), no statistically significant difference between the groups was detected ($p < 0.18$) *(112)*. Nicotine has been shown by several groups to increase the risk of spontaneous abortions *(113–118)*. Accordingly, this study *(112)* attempted to account for the effects of nicotine by matching the nonteratogen-exposed control group with the bupropion group for smoking status and number of cigarettes smoked per day *(112)*. No association between the increase of spontaneous abortions and smoking status was noted in this study. In actuality, there was no difference in the rates of spontaneous abortions among the depressed and smoking women (15.4 vs 16.2%). However, the number of smokers in this study was small ($N = 37$), and further study with a larger sample size is indicated.

5.2.3.3. Trazodone and Nefazodone (Desyrel, Serzone). Trazodone and nefazodone, both of which are phenylpiperazine antidepressants, exert their therapeutic effects via inhibition of central serotonin and norepinephrine reuptake. Nefazodone has reduced affinity for cholinergic and α-adrenergic receptors and is therefore less sedative than trazodone *(109)*.

Presently, one multicenter prospective comparison study evaluating the safety of trazodone and nefazodone during pregnancy is available *(119)*. This study followed 147 women exposed to either drug in the first trimester (52 of whom continued either drug throughout pregnancy) and compared them with two comparison groups, consisting of 147 women each, exposed to other antidepressants or nonteratogens, respectively. Upon completion of the study, there were 121 (82.4%) live births, 20 (13.6%) spontaneous abortions, and 6 (4%) therapeutic abortions. Of the 121 live births, 2 (1.6%) were found to have major malformations. There was no difference in the incidence of major malformations between the drug-exposed and comparison groups. It should be noted, however, that fewer spontaneous abortions were observed in the nonteratogen-exposed control group (8.1%) than in either the trazodone/nefazodone (13.6%) or the antidepressant-exposed group (11.5%). Although the differences in the rate of spontaneous abortions between the groups were not statistically significant, they mirror similar increases seen in studies with other antidepressants (discussed earlier).

5.2.3.4. Mirtazapine (Remeron). Mirtazapine, introduced in the United States in the late 1990s, is a new antidepressant that augments noradrenergic and serotonergic transmission *(111)*. To date, there have been no prospective controlled studies evaluating the safety of mirtazapine

during pregnancy. A Turkish group recently followed the pregnancies of two women exposed to this drug in early and mid- first trimester *(120)*. Both pregnancies resulted in the birth of healthy infants (40 and 39 wk gestation, respectively), one of whom had mild hyperbilirubinemia and mild gastroesophageal reflux that resolved without treatment.

5.2.3.5. Saint John's Wort. Saint John's Wort (SJW) (*Hypericum perforatum)* is the most common herbal therapy for depression in use today *(121)*. The active ingredient, thought to be hypericin, is capable of antidepressant effects via inhibition of serotonin, norepinephrine, and dopamine reuptake *(122,123)*.

SJW is generally considered safer than most currently prescribed antidepressant medications *(124–127)* probably because "natural" or herbal products are considered inherently safer than pharmaceuticals by the general population *(128)*. To date, only two cases regarding obstetric self-medication with SJW have been published *(129)*. Of these cases, follow-up data on only one is available. The woman in this case took SJW from 24 wk gestation until term and gave birth to a normal, healthy child.

5.2.3.6. Monoamine Oxidase Inhibitors. The use of monoamine oxidase inhibitors (MAOIs) in pregnancy has not been well studied, mainly because they are used infrequently as drugs of "last resort" *(130)*. In animal studies, the use of MAOIs in pregnancy has been shown to cause fetal growth retardation *(131,132)*. Human data concerning MAOI safety during pregnancy is limited. A published case series associated MAOI use in pregnancy with an increased incidence of major malformations *(85)*. Specific details concerning the exposures or malformations, however, were unavailable.

Given the discouraging data available, its potential interactions with medications such as terbutaline (hypertensive crisis) *(76)*, and the availability of other more studied antidepressants, MAOI use during pregnancy should be avoided.

5.3. Reported Adverse Outcomes

5.3.1. Poor Neonatal Adaptability

The use of SSRI agents in late gestation has been associated with poor neonatal adaptability, a transient period of jitteriness, difficulty breathing, and some difficulty feeling *(106,133,134)*. As such, infants born to mothers exposed to SSRIs near term should be carefully monitored. These adverse effects are, however, transient, self-limiting generally require no treatment, and appear to have no long-lasting effects on the infants.

5.3.2. Increase in Spontaneous Abortions

Of note, some of the previously mentioned studies reported an increased rate of spontaneous abortions in the antidepressant-exposed groups compared with the nonteratogen-exposed groups. This difference was statistically significant in three of these studies (two on fluoxetine and one on bupropion) *(83,97,112)*. Although the observed rates of spontaneous abortions in any of the antidepressant-exposed groups have not exceeded the reported 10–20% baseline rate in the general population *(82)*, this finding requires further study.

5.3.3. Abrupt Discontinuation Syndrome

Given that at least 50% of pregnancies are unplanned *(102,135)*, many women first become aware of their pregnancies well into the first trimester. These women may abruptly discontinue taking all medications, including antidepressants, in attempts to minimize drug exposure to their fetuses. Einarson and colleagues interviewed 36 pregnant women 1 mo after they received counseling regarding the safety of antidepressant use in pregnancy *(136)*. They found that 34 of these women discontinued their medication abruptly (28 on the advice of their health care providers). Of these women, 26 (70.3%) reported deteriorating physical and psychological health. Eleven of these women reported suicidal ideation, and 4 were hospitalized.

Abrupt discontinuation of certain antidepressants may be associated with a "discontinuation syndrome," characterized by any or all of the following: nausea and vomiting, diarrhea, diaphoresis, hot or cold flashes, tremors, excess lacrimation, syncope, anxiety, panic attacks, low energy, fatigue, and mood swings *(136)*. Most critically, sudden discontinuation of antidepressants has been associated with relapse of the underlying psychiatric condition *(137)*. In the case of antenatal depression, this is of particular concern given the deleterious health effects associated with untreated depression during pregnancy.

5.3.4. Persistent Pulmonary Hypertension in the Newborn

At press time, a newly released case–control study reported a significantly elevated risk of persistent pulmonary hypertension in the newborn (PPHN) in infants exposed to SSRIs following the 20th week of gestation. Although the absolute risk of PPHN in SSRI-exposed infants was relatively low (~ 1 in 100), it was six times higher than that of control group infants. The study findings raise an important concern and should be reviewed carefully during risk–benefit discussions regarding treatment of depression during pregnancy. Children exposed to SSRIs prior to the 20th week of gestation, or to non-SSRIs at any time of pregnancy, were not found to be at an increased risk for PPHN *(138)*.

5.3.5. Directions for Future Study

Despite recent evidence supporting the safety of antidepressant use in pregnancy *(82,83,96–101,105–108,112,119,121)*, several questions remain unanswered.

The sample size in the vast majority of studies assessing the safety of these medications in pregnancy is statistically small. Most studies *(108,112,119)* have only an 80% power to detect a fourfold increase in the risk of major malformations ($\alpha = 0.05$). Almost 800 cases in each treatment group would be required to detect a twofold increased risk, and thousands of cases would be required to detect rare defects.

At present, only one study has assessed the long-term neurodevelopment (i.e., global IQ score, language and behavioral development, and cognitive abilities) of children exposed to antidepressants (fluoxetine and TCAs) *in utero (104)*. Therefore, the long-term effects of *in utero* exposure to these medications (except for fluoxetine) remain poorly characterized. It should be noted that this is an area of active research.

6. CONCLUSION

In this chapter we have reviewed some of the key issues surrounding prenatal depression, including its prevalence, course, and treatment options. Depression during pregnancy is an important issue that cannot be ignored given its high prevalence in general and obstetric populations. It has become apparent, according to data from recent studies, that deleterious effects are associated with untreated depression during pregnancy. Women should not be denied treatment simply because they are pregnant, as there appears to be a relatively safe arsenal of both pharmacological and nonpharmacological treatments available. Women should be given evidence-based information concerning treatment options. Such information would allow them and their health care providers to make appropriate decisions that will ensure the best possible outcomes for themselves and their babies.

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