

Pharmacotherapy of Depression in Pregnancy

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About 20% of pregnant women experience clinical depression. Inadequate treatment of depression has been associated with adverse outcomes in the mother as well as the newborn. Clinicians are often uncertain about pharmacological interventions to treat depressed pregnant women due to concerns regarding fetal exposure to medications. Moreover newer antidepressants with different pharmacological profiles and little data on fetal risk continue to be introduced at a brisk pace. Accumulating data from pharmaceutical registries, cohort studies, toxicology centers, some prospective studies, and case series have permitted certain guidelines for antidepressant use during pregnancy. We review the safety profiles of commonly used antidepressants, discuss clinical decision making based on risk-benefit considerations and make recommendations for pharmacological treatment of depressed women during pregnancy.

Keywords Depression; Pregnancy; Antidepressants; Treatment; Fetus.

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INTRODUCTION

Women of childbearing age have a 10–25% lifetime risk of developing a depressive disorder, with peak prevalence occurring in the age range of 25–44 years (1). About 10–20% of pregnant women experience clinical depression (2). Several factors such as neuroendocrinological alterations, maternal stress, and conflicted attitudes toward pregnancy have been implicated in the development of depression in expectant mothers. Diagnosis of depression can be challenging because the symptoms overlap with those of normal pregnancy (3), and metabolic changes associated with pregnancy can negatively affect mood (4). Women with a history of depression are particularly vulnerable to a recurrent episode during pregnancy. In such women, the risk of a recurrent depressive episode in the first trimester is about 70%, when antidepressant drugs are discontinued prior to conception (5). Depression during pregnancy can also increase the risk for developing postpartum depression, a condition affecting roughly 6.8–16.5 % of all adult women (6). High childbirth burden, elevated trait anxiety, low life satisfaction and lower

social class, and low birth weight of the infant may accelerate the onset of postpartum symptoms (7).

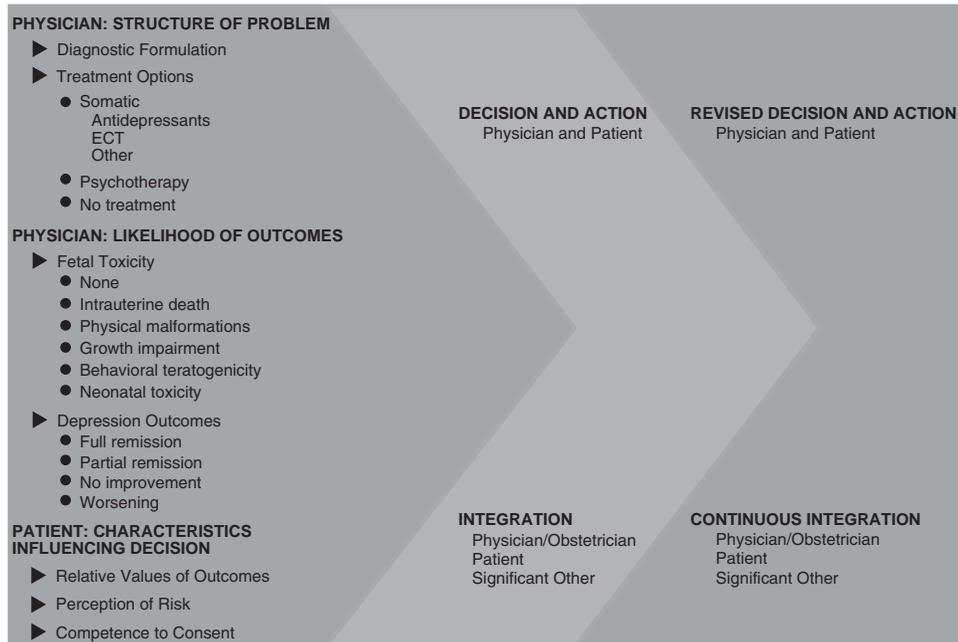
While clinicians agree that depression during pregnancy deserves at least the same degree of attention as depression during other periods of life, they often remain uncertain regarding the nature of pharmacological interventions. This is in large part due to understandable concerns about the effects of fetal exposure to antidepressant drugs. Traditionally, clinicians have felt less reassured about pregnancy data because prospective, double blind, placebo-controlled trials for safety and efficacy of antidepressants have excluded pregnant women. Moreover newer antidepressants with different pharmacological profiles continue to be introduced at a brisk pace; little information is available about fetal risk until the newer agents are utilized for some time. Nevertheless accumulating data from pharmaceutical registries, cohort studies, toxicology centers, some prospective studies, and case series have permitted certain guidelines for antidepressant use during pregnancy. We review the safety profiles of commonly used antidepressants, discuss clinical decision making based on risk-benefit considerations and make recommendations for pharmacological treatment of depressed women during pregnancy.

GENERAL PRINCIPLES OF MANAGEMENT

The clinical situations involving the use of antidepressants during pregnancy include: 1) treatment of depression in women who are planning to conceive; 2) treatment

approaches toward women who conceive while taking antidepressant medications; 3) treatment of a new or recurrent episode of depression during pregnancy; and 4) postpartum treatment of depression. Each of these issues is fraught with decision-making complexities because there are seldom clear answers to questions regarding outcomes for mother and fetus, in both treated and untreated states. Physicians have to balance the risk of untreated depression and the likelihood of relapse if the drug is discontinued, against the potential for harm to the fetus from drug exposure. In a recent review, Stowe contended that “exposure always occurs, be it to treatment or illness,” (8) His advocacy of choosing “the path of least exposure,” when contemplating treatment decisions, is a useful general guideline.

Wisner and colleagues (9) have proposed a useful model to aid the process of decision-making for the clinician and the patient. This is summarized in Figure 1. The model integrates different perspectives to inform the patient in terms of risk-benefit analysis of various treatments. The physician is envisaged as the provider of diagnosis, treatment options, and likelihood of outcomes. The model also outlines the patient variables that may affect the decision process, e.g. competence to consent and perception of the problem. Furthermore, it also recommends that the partner and an obstetrician be closely involved. Proper documentation of the information exchange process between clinician and patient is important. Each case must be individualized to take into account other factors that are known to affect outcome. These include, but are not restricted to; the



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Figure 1 Decision-making process for treatment of depression during pregnancy.

patient's sources of support, substance abuse, adverse life events, socio-economic status, the desire to have the baby, family history, and the natural history of the disease in any given patient (4). Severity of symptoms and the patient's choice weigh heavily on the decision to choose among treatment alternatives.

RISKS OF UNTREATED DEPRESSION IN PREGNANCY

While making treatment decisions, clinicians should not underestimate the adverse consequences of depression. In expectant mothers, inadequate treatment of depression has been linked to self-neglect, poor nutrition, tobacco and alcohol use, lower utilization of prenatal care, and postpartum exacerbation of depression [10]. Also the potential for suicide always remains a major concern with any case of depression. Moreover depression disrupts mother-infant bonding; this may have adverse effects on child development [11]. Studies have found that the maternal depressive state activates the stress response via increased secretion of corticotropin releasing factor and perturbation of the hypothalamo-pituitary-adrenal (HPA) axis [12]. The resulting adverse neuro-hormonal environment has been shown to affect placental function and possibly fetal development [13]. Babies of depressed women have been reported to be born prematurely and/or with low-birth weight [14], and may exhibit short and long-term physical and behavioral complications.

ASSESSMENT OF RISK OF PHARMACOLOGICAL AGENTS

Severe cases of depression, especially with psychosis, poor weight gain, and suicidal ideation, earn an obvious recommendation for pharmacological intervention. However in cases of mild depression or depression in remission with antidepressant treatment, initiation or continuation of pharmacotherapy becomes more complex. While effective pharmacologic agents are available to treat depression, their safety for the fetus is not backed up by sufficient controlled studies. The lack of robust safety data are due to obvious ethical obstacles inherent in conducting such studies, and also from numerous methodological challenges, including difficulty of finding a suitable control group. Also, there is a 2–4% incidence of major birth defects in newborns in the general population (15), and any teratogenic risk attributed to a drug has to be weighed against this baseline risk. Furthermore, although information about reproductive risks in animals is required for approval from the Food and Drug Administration (FDA), intrauterine periods for organ development in animal and humans are not identical. Therefore extrapolation of preclinical data to humans becomes difficult. Given these limitations, it is not surprising that many

Table I FDA Rating System for Use of Medications in Pregnancy

Category A	Controlled studies show no risk. Adequate, well-controlled studies in pregnant women have failed to demonstrate risk to the fetus.
Category B	No evidence of risk in humans. Either animal findings show risk, but human findings do not, or if no adequate human studies have been done, animal findings are negative.
Category C	Risk cannot be ruled out. Human studies are lacking, and animal studies are either positive for fetal risk or lacking as well. However, potential benefits may justify the potential risk.
Category D	Positive evidence of risk. Investigational or postmarketing data show risk to the fetus. Nevertheless, potential benefits may outweigh the potential risk.
Category X	Contraindicated in Pregnancy. Studies in animals or humans, or investigational or postmarketing reports have shown fetal risk that clearly outweighs any possible benefit to the patient.

All SSRI, venlafaxine, nefazodone, trazodone, and mirtazapine are FDA category C, bupropion is category B, amitriptyline and clomipramine are category C, for MAOI, imipramine, nortriptyline and desimpramine, safety in pregnancy and nursing is not known.

clinicians find the FDA's 'use in pregnancy' rating system (Table I) for drugs to be confusing, particularly for psychotropic drugs.

It should be noted that the FDA assessment system for the degree of teratogenic risk uses *available* data. Most antidepressant medications are listed as category C, which imply a chance of harm to the fetus. Also no psychotropic medications are classified Category A which means that either every psychotropic carried some risk or the risk of some agents has not been sufficiently explored. No psychotropic agents have been FDA-approved for use in pregnancy.

MORPHOLOGIC TERATOGENICITY

Due to the ambiguities of the FDA system, a working knowledge of the critical periods of development for each organ system in the fetus helps the clinician to determine the extent of teratogenic risk for a particular drug. It is important to remember that all antidepressants cross the placenta, which means that some degree of fetal exposure always occurs. The penetration of the fetal compartment is influenced by the characteristics of the drug, the dose and the stage of pregnancy. However the rate of placental transfer may be variable for different drugs. Figure 2 summarizes the degree of susceptibility of embryonic organs to potential teratogens during gestation.

The two weeks following fertilization are generally considered safe, as the placenta has not yet formed. Formation of most organ systems is complete by week twelve. The central nervous system is most vulnerable 14–35 days post-conception. Environmental toxins such as drugs, tobacco,

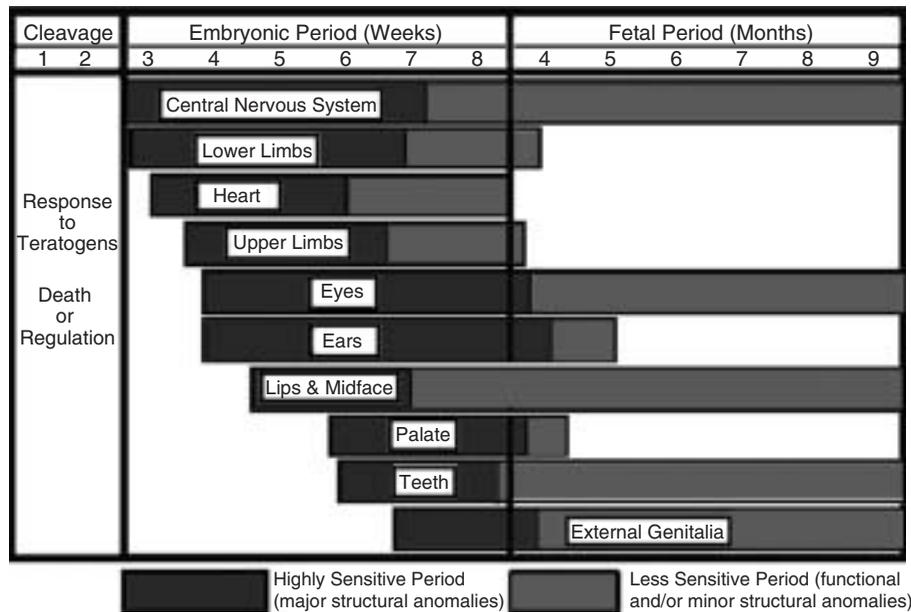


Figure 2 Degrees of susceptibility of embryonic organs to teratogens at different development periods.

and alcohol could conceivably increase the teratogenic potential of ingested medications.

INDIVIDUAL PHARMACOLOGICAL AGENTS IN PREGNANCY

Although the pharmaceutical industry has not promoted the use of medications during pregnancy due to lack of safety documentation, the off-label use of psychotropics in pregnant women has been common for several years. Changes in maternal physiology in pregnancy should be kept in mind while prescribing medications. These include expansion of the volume of distribution, accelerated hepatic metabolism, enhanced renal clearance, and changes in plasma protein binding (16). This translates into increased dose requirement for most antidepressants, especially in the last trimester, to avoid sub-therapeutic blood concentrations (17). However, dose changes in later stages of pregnancy should also consider that several fetal enzyme systems are not mature at birth and may impair the ability of the newborn's liver to metabolize drugs.

Although no definitive data are available, it is believed that the use of antidepressants during pregnancy reflects prescription patterns in the general population. Selective serotonin uptake inhibitors (SSRIs) have been the most widely used because of their established efficacy and favorable side effect profile. However agents such as venlafaxine, bupropion and mirtazapine, as well as tricyclic antidepressants have been preferred by clinicians in certain situations. The safety concerns regarding drug and food interactions have limited the use of Monoamine oxidase

inhibitors (MAOIs). Table II summarizes the antidepressant data in pregnancy.

Selective Serotonin Reuptake Inhibitors (SSRIs)

Among SSRIs, *fluoxetine* (Prozac®) has been most widely studied in pregnancy. Most of the published studies indicate that a mother's use of fluoxetine in the first and second trimester does not increase the rate of obstetric complications or major fetal malformations. Goldstein and colleagues (18,19) used the manufacturer's pregnancy registry to identify all cases of prospective exposure to fluoxetine in the first trimester. The data were compared with that obtained from historic reports of newborn surveys. The overall sample was large and included 969 pregnancies. The fluoxetine exposed women did not show an increased rate of adverse pregnancy outcomes. This data are supported by two recent controlled studies. Hendrick et al. (20) found that the rate of fetal complications in 138 women prenatally exposed to fluoxetine, paroxetine, and sertraline was comparable to that of the general population, despite an association of low birth weight with exposure to high-dose fluoxetine (40–80 mg/day). In another prospective study, Nulman et al. (21) examined the neurodevelopmental effects in children of fluoxetine and tricyclic antidepressant exposure during pregnancy. A control group of non-exposed, non-depressed subjects were also studied. Neither fluoxetine nor tricyclic antidepressants were found to adversely affect cognition, language development, or temperament of pre-school and early school children. However, in an earlier study, Pastuszak et al found that although exposure to tricyclics or

Table II Summary of Studies of Antidepressant Agents in Pregnancy

Study	Drug	Sample size	Study focus	Study outcome
(20)	Fluoxetine Sertraline Paroxetine Fluvoxamine Citalopram	73 36 19 3 7	Birth outcomes	Rates of fetal complications not higher than general population. Increased incidence of low birth weight with high dose fluoxetine 40–80 mg/day.
(21)	Fluoxetine Tricyclics	40 46	Effects on IQ, language development and cognition	No adverse effects observed in either group.
(23)	Fluoxetine	228	Birth outcome	Late exposure associated with premature labor and poor neonatal adaptation.
(29)	Paroxetine Fluvoxamine Sertraline	97 26 147	Birth outcome	No increased risk for major malformations, miscarriages, stillbirths, or prematurity.
(31)	Paroxetine Fluoxetine controls	118 118 629	Birth outcomes	No differences in birth weight and prematurity. Higher miscarriage rate with fluoxetine.
(27)	Fluoxetine Citalopram	10 10	Perinatal sequelae of SSRI exposure	Neonatal adaptation problems in exposed newborns.
(24)	Fluoxetine	64	Birth outcome after 1st and 3rd trimester exposure	More special nursery admissions in 3rd trimester exposure group.
(18,19)	Fluoxetine	969	Incidence of birth defects	Not greater than that observed for general population.
(22)	Fluoxetine Tricyclics Controls	128 128 128	Birth outcome	Slightly increased incidence of miscarriage in Fluoxetine and tricyclic group.
(41)	Tricyclics Fluoxetine Paroxetine Sertraline controls	209 129 28 32 398	Birth outcomes	No difference between TCA, SSRI and controls in rate of malformations or complications. SSRI exposure in 3rd trimester associated with lower APGAR scores.
(93)	Citalopram + controls	11 + 10	Birth outcome	Comparable outcomes in citalopram exposed and control newborns.
(34)	Paroxetine Controls	82 27	Birth outcome in 3rd trimester exposure	Increased rate of neonatal complications with 3rd trimester exposure.
(30)	Citalopram Paroxetine Sertraline Fluoxetine Non SSRI	375 122 33 16 423	Delivery outcome after antidepressant use in early pregnancy	No adverse birth outcomes.
(114)	SSRI controls	18 + 20	Infant development at 2, 3 & 8 months	No effect of SSRI exposure on infant development.
(45)	Nefazodone Trazodone	58 89	Birth outcome after 1st trimester exposure	No increased incidence of major malformation, premature labor, and low birth weight.
(43)	Venlafaxine controls	150 150	Risk of major malformations	None. But slightly higher rate of spontaneous abortion in Venlafaxine group.

fluoxetine did not increase the incidence of major malformations, it did increase the incidence of miscarriage in both groups (22).

Although the data are not consistent, some studies have suggested that taking fluoxetine in the third trimester may increase the rate of newborn complications and neonatal adaptation problems. A frequently cited study by Chambers et al. (23) prospectively identified 228 women taking fluoxetine and contrasted their pregnancy outcomes with 254 women not taking the drug. The results showed an association of late trimester fluoxetine exposure with premature labor and poor neonatal adaptation. This study did not

control for the potential confounding effects of severity of depression and maternal age. In another study, Cohen et al. (24) found that third trimester exposure to fluoxetine was related to a 3-fold higher rate of newborn complications compared with the first- or second-trimester exposure. Case reports have attempted to characterize newborns' symptoms after fluoxetine exposure during pregnancy (25,26). The reported symptoms include shivering, crying, irritability, and sleeping difficulties. There has been a debate over whether these symptoms reflect a neonatal withdrawal syndrome after abrupt cessation of exposure to SSRI at delivery or if they are simply caused by serotonergic overstimulation

of the fetus during pregnancy. Laine et al. (27) attempted to address this question in a recent prospective controlled trial that matched 20 mothers receiving fluoxetine or citalopram (20–40 mg) with 20 controls and also measured cord blood concentrations of the drugs and serotonin metabolites. The study reported increased risk for serotonergic adverse effects during the first few days of life in newborns of mothers taking fluoxetine or citalopram during third trimester. However the symptoms subsided quickly without any specific treatment. The relationship between declining drug concentrations and resolution of the symptoms indicated that the mechanism may be CNS serotonergic overstimulation rather than a SSRI withdrawal syndrome. Despite a long half-life, withdrawal symptoms have been reported in the fetus when exposure to fluoxetine ceases at delivery (28). Continuing the medication is still probably the safest course of action, especially if risk of depressive relapse in the mother is judged to be high.

The safety of *paroxetine* (Paxil® and Paxil CR®), *sertraline* (Zoloft®), *fluvoxamine* (Luvox®) and *citalopram* (Celexa®) during early and mid pregnancy has also been well-documented, although the data are not as extensive as that for fluoxetine. The manufacturer reviewed over 1,100 reports of patients who were treated with paroxetine during pregnancy, most of whom were exposed during the first trimester. Overall, the pattern of congenital abnormalities was similar to that reported in the general population and there was no unexpected clustering of abnormalities among the reports. Kulin et al. (29) followed 267 women exposed to SSRIs in a prospective controlled multicenter study. Paroxetine, sertraline and fluvoxamine did not increase the risk of major malformation, miscarriages, stillbirths, or prematurity. Similarly in a prospective study using the Swedish birth registry, first trimester exposure to citalopram was not associated with an increase in birth complications in 375 infants (30). The same study showed comparable safety results for paroxetine (122 cases), sertraline (33 cases), and fluoxetine (16 cases). Three additional prospective studies further support the absence of teratogenic risk with paroxetine, sertraline, fluoxetine and fluvoxamine (31,32,33). As yet, there are no studies examining the safety profile of escitalopram (Lexapro®; citalopram's recently introduced enantiomer) in pregnancy, although it is classified as category C by the FDA.

The effects of paroxetine and sertraline in the third trimester have also been explored. Costei et al. (34) compared the perinatal outcomes of infants exposed to paroxetine during the third trimester to two matched control groups: 55 women–infant pairs exposed to paroxetine during the first and second trimesters and healthy controls. Third trimester exposure to paroxetine was associated with a higher rate of preterm labor and perinatal complications requiring prolonged hospitalization, compared to controls. Some of those complications included respiratory distress, hypoglycemia, and jaundice. Sertraline use in the third trimester has also been believed to

increase the risk for prematurity and admission to special care nurseries (35). There has been limited data comparing the extent of fetal exposure when SSRIs are taken in late pregnancy. Hendrick et al. (36) measured drug and metabolite concentrations in both maternal and umbilical cord sera in 38 women taking sertraline, fluoxetine, citalopram, and paroxetine. Mean ratios of cord to maternal serum concentrations of antidepressants and their metabolites were used as an index of exposure. Values ranged from 0.29 to 0.89. Sertraline and paroxetine produced the lowest ratios, citalopram and fluoxetine produced the highest ratios. Notably, none of the infants were born preterm or of low birth weight. Moreover, there was no evidence of accumulation of medications in the fetal circulation.

Third trimester exposure to paroxetine has been found to produce withdrawal symptoms in the neonate such as jitteriness, increased muscle tone, tremors and irritability (37,38). Case reports have also linked maternal use of sertraline with withdrawal symptoms in the infant (39). Some clinicians in an effort to avoid withdrawal symptoms in the newborn, taper off the SSRI several days or weeks prior to the expected delivery date. Despite the potential for development of SSRI withdrawal syndrome in the neonate (40), the symptoms are seldom serious and appear to resolve spontaneously. Discontinuation may therefore be unnecessary, and the mother is spared the risk of entering the postpartum period without medication coverage.

Tricyclic Antidepressants

Despite the introduction of SSRI and newer agents, tricyclic antidepressants continue to have a place in the treatment of depression, particularly among patients who fail to respond to or tolerate SSRIs. Studies have found the overall safety of tricyclics in pregnancy to be comparable to that of SSRIs (41). Amitriptyline and clomipramine have been listed as FDA category C while the FDA considers imipramine, nortriptyline and desipramine as 'safety in pregnancy not known.' Information derived from over 400 incidences of first trimester exposure to tricyclics have failed to demonstrate any excess of congenital anomalies (42). A recent comprehensive review (4) reported that three prospective and more than ten retrospective studies failed to implicate tricyclics in congenital malformations or abnormal child development. Cases of tricyclic withdrawal in neonates have been described in the literature but are seldom serious except for possibly, that associated with clomipramine (4).

Other Antidepressants

Although there are relatively less data, the risk of teratogenicity with exposure to other antidepressants seems at

least comparable to SSRI and tricyclics. *Venlafaxine* (Effexor®, and Effexor XR®), a serotonin and norepinephrine uptake inhibitor commonly used in clinical practice, is rated category C by the FDA. In a prospective, controlled, multi-center study, no risk of major fetal malformations was found for a group of 150 women exposed to venlafaxine, compared to a control group consisting of 150 women who took another SSRI and a non-teratogenic drug (43). There was a slightly higher rate of spontaneous abortion in both the venlafaxine and SSRI groups, whether this was related to medication or to depression was unclear. The effects of venlafaxine on child development remain to be clarified. Discontinuation syndrome may occur upon abrupt cessation of venlafaxine and adversely impact the infant (40). Unlike other antidepressants, *bupropion* (Wellbutrin®, Wellbutrin SR®, Zyban®) is rated category B by the FDA. Pearson et al (44) reviewed the obstetrical and neonatal records of 70 infants born to mothers exposed to bupropion, venlafaxine, SSRIs (fluoxetine, paroxetine and sertraline), and tricyclics (nortriptyline, imipramine, desipramine, amitriptyline and clomipramine) during pregnancy and/or labor. The medical records were blindly scored by two different raters with respect to the presence of obstetrical complications and perinatal outcomes including APGAR scores, birth weight, gestational age, and admission to the Special Care Nursery. No treatment-emergent adverse events were identified in infants exposed to any of the antidepressants. In a multicenter study, first trimester exposure to *nefazodone* (serazone®) and *trazodone* was not associated with increased risk of fetal malformations compared to exposure to other antidepressants and nonteratogenic drugs (45). Both are FDA category C drugs. Of note, nefazodone carries a black-box warning for hepatotoxicity, that may limit its use in the future. There are no data for use of *mirtazapine* (remeron®) (FDA category C) in pregnancy or lactation.

Monoamine Oxidase Inhibitors (MAOIs)

Although it is preferable to avoid starting MAOIs during pregnancy due to their side effects, clinical judgment should determine the continuation of treatment in women who conceive while taking MAOI. Reproductive safety of MAOIs such as phenelzine and tranlycypromine and Monoamine Oxidase B Inhibitors such as selegiline (46,47) cannot be inferred from the literature, as there are few publications in that area (48). Recently Reversible Inhibitors of Monoamine oxidase A (RIMAs) such as moclobemide that diminish the potential for food and drug interactions have become available in Europe. A case report showed that Moclobemide treatment had no adverse effects on the fetus of a woman who took moclobemide throughout pregnancy at a dose of 300 mg/day (49).

Mood Stabilizers

In contrast to major depression, the treatment of bipolar depression during pregnancy often involves making decisions regarding prescription of mood stabilizing drugs. Anticonvulsants and lithium are commonly prescribed mood stabilizers. The risks of these medications must be weighed against the 40–50% risk of relapse of bipolar illness following medication discontinuation.

Traditional Anticonvulsants

Valproate (Depakote®) and *carbamazepine* (Tegretol®), two anticonvulsants that are commonly used as mood stabilizers are teratogenic, especially in the first trimester, and when used in combination or in higher doses (50). They are classified as category D by the FDA indicating that studies have found positive evidence for fetal risk, but the potential benefits of the drugs may still outweigh the risks. Both valproate and carbamazepine carry a 1–5 % risk of causing neural-tube-defects such as spina bifida and craniofacial abnormalities in the exposed babies, and may also increase the risk for bleeding tendencies in the newborn (51). Minor malformations such as depressed nasal bridge and fingernail hypoplasia have also been reported in infants exposed to the two drugs. Women of childbearing age who take valproate or carbamazepine must be made aware of the risks to the fetus. High-resolution ultrasound at 16 to 18 weeks of gestation should be performed in women taking these medications in the first trimester (51). In addition, α -fetoprotein levels should be measured to assess for neural tube defects, followed by amniocentesis (51). Folic acid and vitamin K supplementation is recommended during pregnancy to prevent valproate induced coagulopathies (51).

Lithium

Lithium is also categorized as ‘D’ by the FDA. Some authors prefer it over valproate and carbamazepine if the clinical situation warrants the use of mood stabilizers during pregnancy. Lithium has been reported to have a 20-fold higher risk to cause cardiovascular malformations such as Ebstein’s anomaly in the fetus than the general population risk, but the absolute risk remains low (0.1%) (52). Women taking Lithium in the first trimester should undergo fetal echocardiography and ultrasound examination at 16 weeks of gestation (51). Hypotonia, lethargy, and cyanosis, the so called ‘floppy baby syndrome’ is a rare but feared complication in infants exposed *in utero* to lithium (52). Neonatal hypothyroidism and nephrogenic diabetes insipidus may also occur. The hydration status of both mother and infant must be meticulously followed. Maternal serum Lithium levels

should be maintained at no higher than 0.9 mEq/L in the last antepartum month, in order to avoid toxicity secondary to the sudden, large fluid shifts that tend to occur at delivery (52).

Newer Anticonvulsants

Lamotrigine (lamictal®) has been shown to be efficacious in randomized, double blind, placebo-controlled trials in the maintenance treatment of manic and recently depressed bipolar patients (53). Although not approved for the short-term treatment of mood episodes, lamotrigine has shown efficacy in the acute treatment of patients with bipolar depression in controlled studies (54). It is categorized as 'C' by the FDA. Results from animal studies using 1.2 times the maximum human recommended dose of lamotrigine (500 mg per day) revealed no evidence of teratogenicity. Data from nearly 950 prospective pregnancies reported to registry maintained by the manufacturer do not suggest a greater proportion of birth defects following lamotrigine exposure compared to that expected in pregnant women with epilepsy (55,56). It should be started slowly as it can induce a serious skin hypersensitivity reaction. Whether this risk is transferred to exposed infants is not known. There have been reports of decreased lamotrigine concentration during pregnancy and restoration of pre-partum concentrations after delivery. Dosage adjustments may be necessary to maintain clinical response. Women taking this medication may be advised to take folic acid supplementation as animal data suggest it may decrease its concentration (51). The efficacy of *gabapentin* (neurontin®), and *topiramate* (topamax®) in the treatment of bipolar disorder has not been demonstrated in randomized, double-blind, placebo-controlled studies.

Antipsychotic Agents

These agents are used to augment response to antidepressants (57), for their putative mood stabilizing properties (58), and for cases of treatment resistant or psychotic depression (59). In such cases, atypical antipsychotics are rapidly becoming the first line agents. Little information exists regarding adverse outcomes in pregnancy and lactation with the use of newer antipsychotics in bipolar disorder. The available data has been summarized in a recent comprehensive review by Ernst and Golberg (51). Studies on small numbers of women have not found any teratogenic effects of *olanzapine* (60,61) or *risperidone* (62,63). *Ziprasidone*, *aripiprazole* and *quetiapine* as yet have no human studies to assess their risk potential. Data regarding older antipsychotics is difficult to interpret because of the confounding effects of underlying psychotic illness. *Haloperidol* (FDA category C) has been studied in hyper-

emesis gravidarum and appears to be generally safe in the first trimester (64). Data regarding phenothiazines are less consistent. A meta-analysis has found that first trimester exposure to phenothiazines may be associated with a slight increase in relative risk of fetal anomalies in some women with schizophrenia (65).

ANTIDEPRESSANTS AND BREASTFEEDING

Postpartum period is a particularly vulnerable period for relapse of depressive disorders and often nursing mothers have to be treated with antidepressants and/or mood stabilizers. Because psychotropic drugs are secreted in breast milk, researchers have investigated the extent and clinical significance of exposure to breast feeding infants. Recent studies have employed the technique of High Performance Liquid Chromatography (HPLC) to directly measure infant serum drug concentrations. This technique is superior over the measurement of the milk/plasma ratio as to assess fetal exposure through nursing (13). The information elicited so far by using this method has indicated that in the majority of cases, antidepressant use is compatible with nursing. Table III summarizes the studies of antidepressants in breast feeding. The adverse effects have been limited to few case reports with fluoxetine, citalopram, nefazodone and doxepin (sinequan®) (66,67,68). Studies have shown that although SSRI and their metabolites accumulate in the breast milk, the excretion rate in breast milk is low and the serum concentrations of the drugs and their metabolites in the infant are significantly lower than that of the mother. In several instances, when the mother was receiving therapeutic doses of SSRI, the concentration of the drug in the infant was minimal or undetectable for fluoxetine (67–74), paroxetine (75–79), sertraline (74,79–81,83–85,87), fluvoxamine (75,89–92) or citalopram (93–97). Moreover, when mother was taking therapeutic doses of sertraline, serotonin transporter blockade in the fetus was found to be far lower than would be expected from that observed in the mother, suggesting that clinical doses of sertraline in the mother do not appreciably affect the fetus (81). Similarly Wisner et al. (98) and Birnbaum et al. (99) have critically reviewed the literature and reported that tricyclic antidepressants were found in

Table III Antidepressants and Breastfeeding

Drug	Infants (N)	References
Sertraline	112	(75,80–88)
Paroxetine	59	(75–79)
Fluoxetine	58	(67–74)
Citalopram	16	(93–97)
Venlafaxine	12	(106–108)
Fluvoxamine	8	(75,89–92)
Nefazodone	3	(102,103)
Bupropion	3	(100,101)

negligible quantities in breast fed infants. Bupropion, nefazodone, moclobemide and trazodone are also minimally excreted in breast milk and appear to be safe in breast-fed infants (100–105). Immediate release venlafaxine and its metabolite O-desmethylvenlafaxine were found to achieve high concentrations in breast milk and the metabolite was detected in a majority of infants in one study (106). However, no adverse effects were noted in the nurslings in this study and several other studies (106–108).

The American Academy of Pediatrics (109) does not feel that maternal use of antidepressants precludes breast feeding, but classifies antidepressants as 'drugs whose effect on nursing infants is unknown'. Although the American Academy of Pediatrics considers valproic acid and carbamazepine to be compatible with breast feeding, several case reports of ill effects to the fetus from exposure to the two medications have prompted some authors to recommend close follow up of pediatric clinical and laboratory variables (51). The breast milk concentrations of lithium were found to be 24–72% of that in the maternal serum in an earlier study (110), a recent study found lower levels and of 0–30% and high degree of variability (111). Nevertheless clinically it seems prudent that breast feeding is avoided in mothers taking lithium. The concentration of lamotrigine in breast milk is about 10% of the weight adjusted maternal daily dose, however no adverse reports have been found in infants (112). Four out of twenty case reports of breast fed infants exposed to olanzapine showed some concerning findings including (shaking, poor sucking, lethargy, protruding tongue, rash, and diarrhea). The manufacturer of olanzapine advises against breast-feeding for those women taking the medication. Risperidone is minimally excreted in breast milk and did not cause any adverse effect in one case report (113). Quetiapine, ziprasidone, and aripiprazole have no data regarding their compatibility with breast-feeding.

Current information does not warrant absolute recommendations on the use antidepressants in nursing women. The risk benefit ratio must be assessed on an individual basis. According to the American Academy of Pediatrics Committee on Drugs, drug exposure in nursing infants can be minimized by the mother taking the medication just after the baby is breastfed or if she knows the baby is due for a long nap. Infants who are breast fed while mothers take antidepressants should be monitored clinically. Monitoring infant serum concentration is not currently the standard of practice, therefore suspecting infant drug-related toxicity on clinical grounds, should indicate discontinuation of nursing regardless of serum levels.

RECOMMENDATIONS AND CONCLUSIONS

Clinicians treating depressed women of reproductive age should recognize that they are likely to be called upon to

make important decisions regarding their medications during pregnancy and lactation. The treatment of depression in pregnancy must occur in collaboration with the patient and her significant other and should be well-documented. Counseling depressed women of childbearing age regarding the risks and benefits of drug treatment should ideally occur prior to conception. If a childbearing woman is not pregnant, clinicians should discuss birth control methods, discuss her plans for conception and provide information about pregnancy-related risks of medications. If and when the woman plans to conceive, she and her significant other should be fully informed about the use of antidepressants in pregnancy and breastfeeding. Decisions about medications should be made jointly by the clinician and the patient. Taper of medications and instituting nonpharmacological treatments may be considered in younger women whose current level of depression is mild, previous history is not incapacitating, and if the impact on self-care and family and social responsibilities in case of relapse is judged to be mild. If the woman conceives while she is off medications and her mood remains stable, medications may be withheld throughout pregnancy and her condition monitored on a regular basis. If the woman relapses after medication taper, medications should be restarted selecting the antidepressant with the least teratogenic option. Currently SSRIs and tertiary amine tricyclics have the most data supporting their safety in pregnancy and lactation. Although the available data show no reason for special concern, newer agents such as venlafaxine, bupropion, nefazodone, and mirtazapine have relatively less information for safety in pregnancy and lactation. For bipolar depression in pregnancy, lamotrigine and lithium seem to be relatively safer alternatives to valproate and carbamazepine. Continuing medications through attempts to conceive may be necessary for a woman who has a history of significant depression-associated impairment.

If a woman become pregnant while taking antidepressants, and is in the first trimester, the specific teratogenic risk/benefit associated with the medication should be discussed and the treatment plan as well as exposure to other medications and toxins should be documented. Continuing the medication may be appropriate if the illness history is severe. Most antidepressants appear to have comparable safety profile; again, SSRI and tertiary tricyclics have the most data. For mood stabilizers, switching to a safer alternative (e.g. valproate to lamotrigine) may be reasonable if there are no contraindications or history of non-response. If the decision is made to discontinue the medications, tapering the medications over a week to minimize withdrawal or rebound symptoms may be more appropriate than abrupt cessation. In such cases clinicians should establish a treatment plan with the patients to consider restarting medications for relapse. If a woman is in her second or third trimester and is taking antidepressants, they may be continued

if the mood is stable. If the woman is symptomatic and not on medications, the clinicians should first establish that the symptoms are related to depression and not other pregnancy-related conditions such as thyroid dysfunction. If a diagnosis of depression is confirmed, restarting medications and continuing them throughout second and third trimester should be considered. Breastfeeding plans and lactation data should be discussed with all women who continue to take antidepressants during pregnancy. Stopping the medication prior to delivery just to avoid neonatal discontinuation syndrome is probably unnecessary. These syndromes are frequently self-limited, and the risk of a depressive relapse in the postpartum period should be considered during such decision-making. Postpartum prophylaxis may be considered in high-risk women or women who remain symptomatic during delivery. This involves continuing or initiating medications at the end of third trimester and continuing throughout the postpartum period. The decision should include discussion of plans to breastfeed.

Finally, further research should include long-term follow-up of children exposed to psychotropic medications to better understand the effects on development, and designing compounds with reduced placental transfer and secretion into breast milk. This should improve treatment approaches toward depressed pregnant and lactating women.

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