

Pharmacologic Treatment of Depression During Pregnancy

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WOMEN OF CHILDBEARING age are at high risk for major depression. The lifetime risk for depression in community samples varies from 10% to 25% for women, with peak prevalence at age 25 through 44 years.¹ Nine percent of pregnant women have illnesses that fulfill Research Diagnostic Criteria for Depression.² In a large sample of women who presented to an urban psychiatric hospital, the proportion of women with episodes of depression during pregnancy or within 3 months of birth was 9%. When the sample was restricted to women who had ever experienced a pregnancy, 1 out of 7 women experienced an episode related to childbearing.³

Despite the frequency of depression in women of childbearing age, information to guide patients and physicians through consideration of treatment during pregnancy is limited. Many women have difficulty obtaining pharmacologic treatment during pregnancy. The problem was highlighted in the lay press in an article in *US News & World Report*: "The baby or the drug? It's a choice that many pregnant women often face—but shouldn't." However, several recent controlled prospective studies of antidepressant use during pregnancy have advanced our knowledge and should be translated into clinical care.

Women consult physicians when they have depression during pregnancy, when

Context Despite the frequency of depression in women of childbearing age, information to guide patients and physicians through a consideration of treatment during pregnancy is limited.

Objective To identify risk factors associated with treatment of major depression during pregnancy to help physicians develop treatment plans that optimize clinical care.

Data Sources Reports of prospective controlled trials in English were identified from MEDLINE and Health STAR using the search terms *antidepressant during pregnancy* and *depression during pregnancy*, by manually searching bibliographies of review articles, and through discussions with investigators for 1989-1999.

Study Selection We selected studies in which maternal and infant health outcomes associated with antidepressant exposure were compared with those of non-teratogen-exposed controls. Four studies published since 1993 were identified and included in the analysis.

Data Extraction We abstracted information about identification of subjects, comparison groups, pregnancy, and birth outcomes. We organized the data along 5 domains of reproductive toxicity: intrauterine fetal death, morphologic teratogenicity, growth impairment, behavioral teratogenicity, and neonatal toxicity.

Data Synthesis Data were available for tricyclic antidepressants (collectively), fluoxetine, and newer selective serotonin reuptake inhibitors (collectively). Exposure to these agents did not increase risk for intrauterine death or major birth defects. Decreased birth weights of infants exposed to fluoxetine in the third trimester were identified in 1 study. The development of children whose mothers took tricyclics or fluoxetine during gestation did not differ from that of controls. Direct drug effects and withdrawal syndromes occurred in some neonates whose mothers were treated with antidepressants near term.

Conclusions Although few in number, new information from prospective studies provides a welcome change from decision making based on nonprospective data. Monitoring and interventions for patients with identified risks (eg, poor weight gain) are recommended.

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an unexpected pregnancy occurs during antidepressant therapy, and when they require maintenance therapy and are plan-

ning a pregnancy. For patients with highly recurrent major depression, recurrence without maintenance therapy is probable,

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with an average (SD) time to recurrence of an episode of 38 (8) weeks.⁵

The American Psychiatric Association provides clinical practice guidelines for major depression disorder in adults.⁶ Effective treatments for major depression include psychotherapy, antidepressant medication, and electroconvulsive therapy. Experienced clinicians and researchers state that chronic or moderate to severe major depression warrants somatic intervention.⁵

METHODS

Reports of prospective controlled trials in English were identified from MEDLINE and Health STAR using the search terms *antidepressant during pregnancy* and *depression during pregnancy*, by manual search of bibliographies of review articles, and through discussions with investigators in the field for 1989 through 1999. We identified 4 prospective studies⁷⁻¹⁰ of antidepressant exposure compared with nonteratogen exposure in pregnant women published since 1993 and abstracted information about study population, design, pregnancy, and birth outcomes. Data were organized along 5 domains of reproductive toxicity: intrauterine fetal death, morphologic teratogenicity, growth impairment, behavioral teratogenicity, and neonatal toxicity.

RESULTS

The incidence of major birth defects in the United States is 2% to 4%; the cause of 65% to 70% of these defects is unknown.¹¹ Anecdotal case reports serve as important sources of warnings about possible teratogenicity; for example, case reports linked a cluster of physical abnormalities and developmental disability to fetal alcohol exposure.¹² However, single case reports cannot establish a drug as the critical etiologic agent. Case-control or prospective studies must be done to evaluate the association between exposure and outcome. Investigators continue to work to isolate the effects of medication exposure from other factors that influence pregnancy outcome.

Framework for Consideration of Reproductive Risk

The toxic effects of fetal exposure to drugs can be organized into 5 domains: intrauterine death,¹³ physical malformations,¹³ growth impairment,¹³ behavioral teratology,¹³ and neonatal toxicity. The period of maximum vulnerability to structural and neurochemical abnormalities of the central nervous system is 14 to 35 days postconception.¹⁴ However, the effects of behavioral teratogens are not limited to this period of neural tube closure.¹⁵ Because most of the formation and elaboration of the mammalian nervous system occurs prenatally, neurotoxic exposure can have extensive post-birth developmental effects. Examples of behavioral teratologic effects are learning problems, abnormal activity levels, and impaired problem solving. Although studies in animals have identified a number of behavioral teratogens, the public health significance of these agents in humans has seldom been investigated. Behavioral teratology differs from direct pharmacologic effects (or withdrawal syndromes) of drugs used near delivery, which is behavioral toxicity in the neonate.

What Is Known About the Teratogenicity of Antidepressants?

In a meta-analysis of 414 cases of first-trimester exposure to tricyclic antidepressants,¹⁶ no significant association between exposure to tricyclic antidepressants (as grouped exposure) and congenital malformations was identified. Four controlled prospective studies of antidepressant exposure during pregnancy have been published since 1993.⁷⁻¹⁰ Pastuszak and colleagues⁷ compared pregnancy outcome following first-trimester exposure to fluoxetine ($n = 128$) with 2 matched control groups: women exposed to nonteratogen ($n = 128$) and tricyclic antidepressants ($n = 74$). Nonteratogens were defined as medications or environmental factors that do not increase the baseline teratogenic risk (such as penicillin or dental x-rays). Women who consulted 1 of 4 teratogen centers during gestation were contacted, and information was collected from the

mother following birth and verified by the child's physician. Women exposed to fluoxetine were age-matched to controls.

The primary outcome was the rate of birth defects in neonates exposed to fluoxetine compared with those exposed to tricyclic antidepressants and nonteratogens. Rates of major malformations were comparable across the 3 groups. Rates of maternal characteristics (age, obstetric history, and alcohol and cigarette use), pregnancy outcome (maternal weight gain, method of delivery, use of forceps, rate of live births, elective abortions, and miscarriages), and offspring characteristics (gestational age and birth weight) did not differ across the groups.

Infants born to women treated with either fluoxetine or tricyclic antidepressants had more neonatal complications than the group exposed to nonteratogens. All 128 women took fluoxetine during the first trimester but only 8 women beyond this point. Therefore, the finding of more neonatal complications in the antidepressant-treated groups of women is not due to direct effects of the medication near term. Some variable associated with taking antidepressants was responsible for the increased neonatal problems. A sustained effect of early exposure or recurrence of maternal depression later in pregnancy are possibilities.

Chambers et al⁸ studied 228 women exposed to fluoxetine and a control group ($n = 254$) of women exposed to nonteratogens (such as acetaminophen, dental x-rays, and limited alcohol ingestion before pregnancy was recognized). The women were recruited from callers to the California Teratogen Information Service. Pregnant women who were exposed to nonteratogens and called closest to the time of the case were recruited as controls. The majority of women were enrolled during the first trimester of pregnancy. The birth outcome was recorded on a standard form completed by telephone interview with each mother shortly after delivery, and medical records were examined.

The investigators divided the population into 2 groups. The first group w-

the early exposure group ($n = 101$), in which exposure occurred before 25 weeks of gestation but not after. Women in the second group (late exposure, $n = 73$) continued to take fluoxetine into the third trimester. Sixty-six of these women took fluoxetine within 2 days of delivery. The rate of major birth defects was not significantly different in the 2 fluoxetine groups compared with controls. However, there were other significant differences between groups. In the fluoxetine groups, the presence of 3 or more minor anomalies (defined as no cosmetic or functional importance) were reported more frequently (15.5%) compared with controls (6.5%; $P = .03$). Premature birth (less than 37 weeks' gestation) occurred in 14.3% of infants born to the late-exposure group compared with 4.1% of infants in the early exposure group, and 5.9% in the control group. When preterm infants were excluded, the rate of admission to a special care nursery was 23% of infants born to the late-exposure group, 9.5% born to the early exposure group, and 6.3% in the control group ($P < .001$). Poor neonatal adaptation (jitteriness, hypoglycemia, hypothermia, poor muscle tone, respiratory distress, weak or absent crying, or desaturation on feeding) was described in 31.5% of the infants born to the late-exposure group compared with 8.9% of the infants born to the early exposure group. Full-term infants born to the late-exposure group had a lower mean birth weight (by an average of 188 g) and shorter birth length than infants born to either the early exposure or control groups. Maternal weight gain was an average of 3 kg less in the late-exposure group. The analysis based on trimester specificity yielded interesting differences, which were not available in the study by Pastuszak et al.⁷

The Toronto Motherisk Group⁹ studied the development of children exposed prenatally to tricyclic antidepressants, fluoxetine, or nonteratogens. Mothers in the control group were chosen from women whose clinical appointments were closest to those of the other groups. At the diagnosis of pregnancy, women were interviewed about medi-

cal history, use of drugs, and obstetrical history. A second interview was done 6 to 9 months after delivery. At this time, the mother was asked to verify duration of treatment with tricyclic antidepressants or fluoxetine during gestation, drug dosage, and perinatal complications. The assessment included a written report from the physician caring for the child.

About one quarter of the population exposed to tricyclic antidepressants ($n = 129$) was lost to follow-up ($n = 24$) or excluded for other reasons ($n = 25$). The study sample consisted of 80 women. Forty women took a tricyclic antidepressant during the first trimester; 36, throughout pregnancy; and 4, at variable times. Eighty-eight women were enrolled in the fluoxetine group; 33 were lost to follow-up, miscarried, elected abortion, or declined further participation so that 55 women and infants were studied. Of this group, 37 women took fluoxetine during the first trimester, and 18 took fluoxetine throughout pregnancy. The control group was 84 children whose mothers had not been exposed to any agent known to affect the fetus during pregnancy. Children in both the study and control groups were between age 16 and 86 months at the time of testing. In a comparison of baseline characteristics, women in the fluoxetine group had more pregnancies, more elective abortions, and lower socioeconomic status. The women in both fluoxetine-treated groups consumed more alcohol and smoked more cigarettes during the index pregnancy than did women in the control group. Baseline measures used to quantify levels of depression and function were similar in the 2 antidepressant groups; however, these measures were not reported for the control group. The infants were assessed by a psychometrician blind to exposure status.

At birth and at the time of testing the percentiles of weight, height, and head circumference of the children in the 3 groups were similar. There were no differences in rates of perinatal complications. Incidence of major malformations was the same in the 3 groups, and mean global IQ was similar. Scores on

verbal comprehension, expressive language, temperament, mood, arousability, activity level, and distractibility tests and behavior problems did not differ in children exposed to antidepressants compared with controls. Multiple regression of the effect of the duration of antidepressant therapy (first trimester compared with entire pregnancy) revealed no significant differences on any of the neurobehavioral tests compared with the control children.

Kulin et al¹⁰ reported pregnancy outcomes following maternal use of the newer selective serotonin reuptake inhibitors (SSRIs) (fluvoxamine, paroxetine, and sertraline hydrochloride). Women who were counseled by a teratogen information service after exposure to 1 of these agents were evaluated in a prospective, multicenter, controlled cohort study. The main outcome measure was the rate of major congenital malformations. A total of 267 women exposed to a newer SSRI and 267 controls exposed to nonteratogens were studied. Exposure to an SSRI was not associated with increased risk for major malformations or higher rates of miscarriage, stillbirth, or prematurity. Birth weights of infants and gestational ages were similar in the group with SSRI-exposure and controls. Pregnancy outcome among women who took an SSRI throughout pregnancy did not differ from those who took the drug only during the first trimester.

The study by Chambers et al⁸ has been criticized because the design was not randomized¹¹; however, due to ethical reasons no randomized controlled trials of antidepressant use during pregnancy have been done. A second criticism was that the older age in the fluoxetine group could explain the excess of poor perinatal outcomes compared with the nonteratogen group.¹⁰ However, the majority of poor perinatal outcomes was in the late-exposure group, which had the same mean age as the early exposure group (32 [6] and 32 [5] years, respectively; controls, 30 [5] years). A third criticism is that the Chambers et al study design⁸ did not allow for separation of the effects of exposure to depression from drug ex-

posure.^{17,18} This issue is inherent in all 4 studies: the drugs of interest (antidepressants) treat an illness (depression) that also affects offspring development.

Controlled prospective data are not available for monoamine oxidase inhibitors or newer antidepressants. However, monoamine oxidase inhibitors are not used widely in clinical practice because of greater hepatic toxicity than newer drugs, the need for a low-tyramine diet, and toxic interactions with other medications. Suggestions for appropriate obstetrical anesthesia and analgesia for women treated with these agents have been published.^{19,20}

The findings of the 4 trials can be summarized around the 5 domains of reproductive risk.

Intrauterine Death

There is no evidence that exposure to tricyclic antidepressants (as a group), fluoxetine, or newer SSRIs (as a group, including sertraline, paroxetine, and fluvoxamine) during pregnancy increases the risk for intrauterine fetal death.

Morphologic Teratogenicity

There is no evidence that tricyclic antidepressants, fluoxetine, or newer SSRIs cause major birth defects in humans or animals. Data from 3 studies^{7,8,10} demonstrated that exposure did not elevate risk for major physical malformations above that in a control group. In the study by Chambers et al,⁸ 3 or more minor physical anomalies occurred more commonly in infants exposed to fluoxetine than in infants exposed to nonteratogens. The authors suggested that multiple minor physical anomalies may be indicative of an effect of fluoxetine on embryologic development that becomes evident in later development. In infants with 3 or more minor physical anomalies (0.5% of infants), 90% have 1 or more major defects as well.²¹ However, the infants exposed to fluoxetine did not have a greater number of major anomalies.

Growth Impairment

Prenatal growth and birth weights of infants exposed to tricyclic antidepressants⁹ and newer SSRIs¹⁰ were comparable to

those of infants exposed to nonteratogens. In the study by Chambers et al,⁸ fetuses exposed to fluoxetine after 25 weeks' gestation had lower birth weights, which were related to lower maternal weight gain. Birth length was also shorter. Newborn growth deficits and poor maternal weight gain associated with fluoxetine were not observed by the Motherisk group.⁹ The reason for the different findings in these investigations is unknown. Until further data accumulate, the recommended clinical action is monitoring weight gain in pregnant women being treated with antidepressants. Weight loss is common in major depression, and undertreated maternal mood disorder could be the factor that affects maternal and infant weights. Poor weight gain dictates diagnostic, nutritional, and behavioral interventions. Self-reported depression symptoms increased the risk of delivering a low-birth-weight infant, having a preterm delivery, or having a small-for-gestational age neonate.²² Maternal depression during pregnancy was associated with unconsolability and excessive crying.²³

Behavioral Teratogenicity

Nulman et al⁹ found no differences in cognitive function, temperament, and general behavior in children prenatally exposed to tricyclic antidepressants and fluoxetine compared with controls. The study is reassuring, and replication studies from other sites would provide greater confidence that the risk of behavioral teratogenicity is low. This domain remains the major area of concern about prescribing central nervous system-active agents during gestation. No information about newer SSRIs or other agents is available.

Neurotransmitters are reliably detected in the developing human brain well in advance of cortical maturation. In the fetal brain, dopamine has the potential to exert effects through classical receptor-ligand interactions, and second messenger systems linked to the receptors are expressed (Alan Unis, MD, written communication, September 3, 1997). In some model systems, activation of second messenger

systems leads to expression of genes governing neural differentiation and, ultimately, neural phenotype. Behavioral teratogenicity is one of the least understood aspects of teratology because animal behavioral models that robustly reflect human drug use are rare.

Neonatal Toxicity

A neonatal withdrawal syndrome has been reported in the offspring of pregnant women treated with tricyclic antidepressants through delivery. Withdrawal symptoms include transient jerky movements and seizures,^{24,25} tachypnea, tachycardia, irritability, feeding difficulties, and profuse sweating.²⁶ Direct anticholinergic effects, such as gastrointestinal stasis and bladder distention,²⁷ have been described in newborns.

The study by Chambers et al⁹ provides data about direct effects of fluoxetine on infant outcome at birth. The recorded neonatal symptoms were similar across multiple hospitals and were comparable to adverse effects seen in adults. These effects were not noted in the study by Pastuszak et al⁷ because the exposures did not allow trimester-specific analyses; however, the effects also were not found in the studies by Nulman et al⁹ or Kulin et al.¹⁰ Similar transient neonatal difficulties have been described in infants exposed prenatally to sertraline.²⁸

Fluoxetine has a long half-life, and neonates may have difficulty clearing the drug. A clinical action to consider is tapering to a lower dosage or discontinuing fluoxetine 10 to 14 days prior to the due date to reduce the risk of direct drug effects in the newborn. Tapering any drug dose prior to delivery will minimize the fetal load at birth.²⁷ The advisability of this maneuver will vary according to the woman's clinical situation. Since delivery cannot be accurately predicted, early dose tapering carries the risk of recurrent depression in a woman facing labor.

Physiologic changes that contribute to increases in dose requirements across pregnancy are primarily enhanced hepatic metabolism and increased volume of distribution, although changes in protein binding and gastrointestinal ab-

sorption also occur.²⁹ A case series of 8 women³⁰ found that the dosage of tricyclic antidepressants must be increased to maintain both clinical response and therapeutic serum levels across gestation and that³⁰ rapid acceleration of the dose requirement occurred in the third trimester. The final dose achieved during gestation ranged from 1.3 to 2 times the dose when the patients were not pregnant, with an average increase of 1.6. The cytochrome P-450D6 isoenzyme is induced during pregnancy,³¹ and anatomic studies have demonstrated proliferation of the endoplasmic reticulum of the hepatocyte during the last trimester of pregnancy.³²

If a woman has been treated with tricyclic antidepressants during pregnancy, she should receive the dosage she took when not pregnant in the immediate postpartum period. If the dosage is unknown, her final dosage in pregnancy should be reduced by about one third. Adverse effect profiles should be carefully followed through the first 6 weeks after delivery because a diminished capacity to metabolize tricyclic antidepressants has been described during the early postpartum period.³³ Similar data for SSRIs have not been published.

Physicians who care for pregnant women tend to be conservative, which often translates into dose minimization during a time of increased dosage requirement for some drugs. However, allowing a woman to be symptomatic during pregnancy can result in unacceptable costs to the woman and fetus.

IMPLEMENTATION OF SOMATIC TREATMENT

The biological dysregulation associated with depression is not an ideal milieu for pregnancy. Two studies by Sandman et al.^{34,35} demonstrated that, independent of biomedical risk, perceived life-event stress and anxiety in pregnancy significantly predicted infant birth weight and gestational age at birth and that low birth weight and prematurity were mediated by peptides derived from the activated hypothalamic-pituitary-adrenal (HPA) axis, including adrenocorticotrophic hormone and β -endorphin. Activation of the

HPA axis is one of the most reproducible findings in neuroendocrine studies of major depression in patients who are not pregnant.³⁶ In animal models, stress independent of chemical agents causes fetal hypoxia, low birth weight, decreased litter size, miscarriage, and fetal hypotension.³⁷

Severity of maternal depressive symptoms is an important factor in the risk-benefit decision-making process. Poor weight gain or frank weight loss and malnutrition during pregnancy puts infants at risk for low birth weight. Suicidality must be carefully assessed. Psychosocial consequences include long-term hospitalization, marital discord and divorce, inability to engage in obstetrical care, difficulty caring for other children, and loss of employment.

Demonstrated efficacy (with minimal adverse effects) in an individual patient improves the likelihood of response to the agent, and maternal recovery from depression can justify fetal exposure. Wisner and Perel³⁷ identified nortriptyline as a favorable tricyclic antidepressant during pregnancy because of its long history of use; lower relative anticholinergic potency compared with other tricyclic antidepressants; and well-studied relationship between plasma concentration and therapeutic effect, which has been investigated in pregnancy.³⁸ However, if a woman has responded well to another tricyclic antidepressant, preferential consideration should be given to the use of the drug known to be effective.

Because of the low toxicity of fluoxetine and other SSRIs, many women have tried and responded to these medications. The same considerations about known response and minimal adverse effects for an individual patient can be applied to these agents. Whether to use an SSRI with a shorter half-life because of findings⁸ of neonatal complications that may be due to fluoxetine remains an issue. This strategy is premature because data about fluoxetine conflict, and data are lacking for other SSRIs used near term. Preliminary data for sertraline suggest similar neonatal difficulties. The use of newer agents with limited safety data puts pa-

tients at risk for unknown adverse effects. The limitations of knowledge about new drugs must be thoroughly presented by physicians and weighed by patients in the decision-making process.

Whether to treat a woman with a newer agent to which she is known to respond but which has not been studied prospectively is another issue. Limitations of knowledge about a drug may cause a patient to choose an agent that has been evaluated prospectively. Alternatively, the risk of nonresponse may lead the patient to request a less well-studied agent that is effective for her.³⁹

Prescription drugs must include information about effects during pregnancy and lactation. To summarize the teratogenicity of drugs, the Food and Drug Administration (FDA) developed 5 categories of risk coded A, B, C, D, and X.⁴⁰ Most antidepressants are in Category C (the largest category), which includes both drugs with demonstrated adverse reproductive effects in animals and drugs for which there are no studies in humans. A multidisciplinary task force currently is developing new guidance documents on the interpretation of reproductive toxicity data from animal and human exposures to revise the categorization scheme.⁴⁰

Exposure to alcohol and other drugs (including nonprescription drugs) is common during pregnancy and must be documented prior to prescribing antidepressants. Identification and treatment of substance abuse improves pregnancy outcome.⁴¹ Smoking also affects obstetrical outcomes.⁴² Careful notation is important to avoid selective implication of the antidepressant if a negative outcome occurs. The woman's history may suggest the possibility that medications for obstetrical problems, such as premature labor or hypertension, are likely to be prescribed after treatment with an antidepressant has been implemented. Guides to interaction of SSRIs with commonly prescribed agents in general medicine are available.^{43,44}

Use of a patient self-report or clinician-administered depressive symptom rating scale is advisable to assess depression. Systematic evaluation of the patient's depres-

sive symptoms and functional level serves to document clinical status. The measure can be repeated to assess response to the intervention. The Inventory to Diagnose Depression⁴³ is a useful self-report form because it establishes diagnostic criteria and symptom levels for depression and has a separate monitoring form. The clinician-administered Hamilton Rating Scale for Depression⁴⁴ is the standard for clinical trials. Functional ratings can be established with the use of the Clinical Global Impressions,⁴⁵ a 7-point global severity and change scale, or the Global Assessment Scale, which measures overall functioning on a scale from 1 to 100.⁴⁶

CONCLUSIONS

New information derived from prospective studies about the management of depression during pregnancy provides welcome relief from decades of decision making based on nonprospective, uncontrolled data. However, more research is needed. Epidemiologic studies provide conflicting information about fluoxetine use during pregnancy. Complementary clinical studies will determine whether poor maternal weight gain is due to fluoxetine or depressive symptoms that either do not or only partially respond to fluoxetine. If shown to be directly induced by fluoxetine, low maternal weight gain may be treatable. No data-based strategies for management of drug therapy near term exist. Additional studies are needed to bring evaluation of the risk for behavioral teratogenicity of antidepressants to new levels of sophistication. Experience with recently marketed agents also must be studied systematically. Data from women and infants exposed to these new agents should be collected, or these valuable experiences will be lost to others who must make risk-benefit decisions. We hope that this review will be a catalyst for improvement in the care of pregnant women with depression.

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