# Use of antidepressants during pregnancy and lactation

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## ABSTRACT

The prevalence of depression among pregnant women has been estimated to be 7 to 19 percent. Untreated depression has been associated with poor outcomes for both the mother and neonate. Antidepressant use during pregnancy has been associated with similar outcomes. This review will evaluate the risks and benefits of antidepressant use during pregnancy and lactation.

## KEYWORDS

pregnancy, lactation, antidepressants

## INTRODUCTION

The prevalence of depression among pregnant women has been estimated between 7 and 19 percent.[1] Several risk factors have been identified for depression during pregnancy including past history of depression, having anxiety, low socioeconomic status, lack of social support, unplanned pregnancy, being single, and exposure to domestic violence.[2] Untreated depression has been associated with poor outcomes, including preterm delivery, low birth weight, and inadequate prenatal care.[1-3] It has been correlated with decreased self-care, which could be reflected as poor eating habits, or use of alcohol and tobacco, all of which may affect the fetus.[1-3] Although the risk is low, use of antidepressants during pregnancy has been linked to outcomes similar to those observed with untreated depression .[2] It is important to understand the risks and benefits of using antidepressants in this population.

## ANTIDEPRESSANTS IN PREGNANCY

Data regarding the use of antidepressants during pregnancy have been inconsistent. This may be related to the observational nature of the studies, as confounding factors (e.g. dose, length of exposure, tobacco, drug, and alcohol use) could not be controlled.[3, 4] Congenital malformations have not been conclusively linked to a specific antidepressant, or class of antidepressant, with the possible exception of paroxetine.[3] However, this should not be interpreted that using other antidepressants during pregnancy is without risk.

The most frequently prescribed antidepressant class during pregnancy is the selective serotonin reuptake inhibitors (SSRIs), followed by serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and rarely monoamine oxidase inhibitors (MAOIs).[2] The majority of antidepressants are pregnancy category C. Most studies conducted on SSRIs have found no increase in malformations, but exposure to SSRIs may present a small increased risk.[4] Among the SSRIs, fluoxetine is the most studied, and the majority of studies have found no association with increased risk of malformations.[4] Clinicians, however, should take into consideration its long half-life and possibility of accumulation in the neonate, and higher infant plasma levels when breastfeeding than most antidepressants.[4] For these reasons, it is generally not used as a first line agent during pregnancy.[4] Sertraline and citalopram are generally considered safe during pregnancy.[4] Composite data with sertraline demonstrated no increased risk of malformations with exposure in utero, but one study found an increased risk of omphalocele (OR 5.7, CI 1.6-20.7) and septal defects (OR 2.0, CI 1.2-4.0).[4] Sertraline may be considered a first line choice, due to its data during pregnancy, as well as safety during lactation.[4] Citalopram exposure was associated with malformation rates similar to the general population in 5 studies.[4] However, one study found an increased risk of anencephaly, omphalocele, and craniosynostosis (OR 2.53, CI1.04-6.10).[4] Exposure to venlafaxine or duloxetine during pregnancy does not appear to increase risk of congenital abnormalities.[4]

In 2005, the Food and Drug Administration (FDA) released a public health advisory regarding the use of paroxetine during pregnancy. The advisory was based on two studies that demonstrated an increased risk of cardiac malformations with exposure to paroxetine during the first trimester.[5] One study based on the Swedish national registry data demonstrated a two-fold increased risk of cardiac malformations when compared to all infants (OR 2.22, CI 1.39-3.55, absolute risk 2 percent vs. 1 percent).[4,5]

Additionally, a review of United States insurance claims data found a 1.5 fold increased risk of cardiac malformations when compared to infants exposed to other antidepressants.[5] At that time paroxetine was designated as a pregnancy category D drug.[5]

In 2006, the FDA published an advisory to inform of the possible link between SSRI use during pregnancy and persistent pulmonary hypertension (PPHN).[6] The base rate of PPHN is 1-2 per thousand infants and is fatal in about 10 percent.[3, 7] Two studies showed an increased risk, yet three others found that exposure to antidepressants does not appear to increase this risk.[7] One study of 1.6 million births found an absolute risk increase from 1.2 per thousand to 3 per thousand with SSRI exposure.[2] Due to this conflicting information, in 2011 the FDA stated that there is not enough evidence to conclude that SSRI use during pregnancy causes PPHN.[7]

Bupropion exposure during pregnancy has produced inconclusive data regarding congenital malformations. The manufacturer's registry reported outcomes on 724 first trimester exposures; 579 live births without congenital abnormalities, 17 live births with abnormalities, 90 spontaneous abortions, and 30 elective abortion (6 with birth defects).[4] Cardiac malformations were of concern, however, it was determined that the data were not adequate to associate bupropion with an increased risk of cardiac malformations, or other birth defects.[4] Two retrospective controlled studies compared data of women who filled prescriptions for bupropion or other antidepressants during the first trimester and found no increased risk of congenital malformations in the bupropion group when compared to other antidepressants.[4] Bupropion is not considered a first line treatment during pregnancy, but may be useful in women who are depressed and have failed non-pharmacological treatments for smoking cessation.[4]

Data regarding the use of trazodone or mirtazapine during pregnancy are limited. Trazodone demonstrates pregnancy outcomes similar to unexposed pregnancies.[4] One observational study reported 41 first trimester exposures to mirtazapine. Within the 41 pregnancies, there were eight spontaneous abortions, eight pregnancies terminated for medical reasons four preterm deliveries, and one unknown outcome.[4] Another study of 104 pregnancies exposed to mirtazapine (95% first trimester exposures) found two major malformations including patent ductus arteriosus and midline facial defect.[4]

As with SSRIs, most studies have found no association between TCAs and congenital abnormalities.[4] Nortriptyline and desipramine are preferred, due to fewer cardiac, sedative, and gastrointestinal side effects in the fetus.[4] MAOIs are generally not recommended during pregnancy due to association with fetal growth restriction in animal studies.[4] The risk of hypertensive crisis would also be of concern.

The American Psychiatric Association (APA) and the American College of Obstetricians and Gynecologists (ACOG) published a report in 2009 to help guide treatment of depression during pregnancy.[3] The report contains treatment algorithms for women considering pregnancy, pregnant women currently treated with medication for depression, and pregnant women not currently on medication for depression. In this report, psychotherapy is recommended as a first line approach to treating mild to moderate depression in pregnant patients not currently prescribed antidepressants.[3, 4]

Women who prefer medication should be educated on risks and benefits of treatment. Based on the current data, antidepressants should be avoided in the first trimester, if possible.[2,3] Patients treated with antidepressants should be treated with a single medication at the lowest effective dose.[8] Medication choice should also take into consideration safety during lactation.[4] Women should be informed that peripartum exposure to SSRIs and TCAs has been associated with temporary neonatal withdrawal symptoms.[3,4] The withdrawal symptoms associated with TCA exposure include jitteriness, irritability, and rarely seizures.[3] The withdrawal symptoms associated with SSRI exposure include tachypnea, temperature instability, hypoglycemia, weak or absent cry, and seizures.[3] These symptoms are transient and usually resolve within two weeks after birth.[3] All adverse events related to antidepressant use during pregnancy should be reported to the FDA Med Watch program.

Pregnant patients currently treated with antidepressants, who wish to discontinue, should be evaluated for risk of relapse, history of suicide attempts, and severity of depression prior to tapering the medication. Medication discontinuation may not be appropriate in women with severe, recurrent depression, even if currently asymptomatic. One prospective study found a six- fold higher risk of relapse among women with recurrent depression who discontinued antidepressants during pregnancy when compared to those who continued treatment.[3] Those who have psychosis, or a history of

suicide attempts may also not be appropriate for medication discontinuation.[3]

## NON-PHARMACOLOGICAL TREATMENTS

Some women may decline antidepressants during pregnancy. Psychotherapy should be offered to all women, as monotherapy or in conjunction with antidepressants. Both individual and group modalities have been proven efficacious.[3,4] Electroconvulsive therapy (ECT) is also considered safe and effective in managing severe depression during pregnancy.[3,4,8] ECT may be indicated if there is no response to medications, and in suicidal or psychotic patients.[3] Some evidence has also proven light therapy to be an efficacious non-pharmacological treatment in this population.[4]

## LACTATION AND ANTIDEPRESSANTS

As with treatment during pregnancy, treatment during lactation should be based on risks and benefits for both the mother and infant.[9] The American Academy of Pediatrics Committee on Drugs considers antidepressants "drugs in which effects are unknown, but may be of concern in breastfeeding".[10,11] All psychotropic medications can enter the breast milk, and therefore may transfer to the infant.[8-10] Of the antidepressants, bupropion, duloxetine, fluvoxamine, paroxetine, and sertraline are undetectable in infant plasma levels.[9] Escitalopram results in undetectable to very low levels in infant plasma and is therefore preferred over citalopram.[9,12] Fluoxetine and venlafaxine demonstrated the highest infant plasma levels.[9]

Some case reports have documented adverse events related to infant exposure to antidepressants through breast milk.[9] The majority of reports are related to exposure to fluoxetine or citalopram.[9] Adverse events included decreased feeding, irritability, crying, and watery stools with fluoxetine, and colic, decreased feeding, and sleep difficulties with citalopram.[9] There is no evidence to support altering dosing times or pumping and discarding milk.[9] Testing breast milk or infant serum concentrations is not generally indicated.

In general, most women should be advised to continue breastfeeding while using antidepressants, as the benefits outweigh the risks for most medications.[9,10] Escitalopram and sertraline are preferred over other SSRIs during breastfeeding, due to lower infant exposure, and should be considered first-line during breastfeeding in women not currently treated with an antidepressant.[9,12] Paroxetine is an acceptable choice during breast feeding, however, providers should take in to account the possibility of future pregnancy due to associated risks as stated previously.[12] Fluoxetine and citalopram produce higher infant plasma levels, and should be used with caution.[9,12] However, women treated with fluoxetine or citalopram during pregnancy should continue these medications during lactation rather than switching to another agent due to the increased risk of relapse.[9,12]

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**How to cite this article**
Norris MM. Use of antidepressants during pregnancy and lactation. Ment Health Clin [Internet]. 2013;3(2):58-60. Available from: http://dx.doi.org/10.9740/mhc.n163520