Depression and Anxiety in Pregnancy

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ABSTRACT

The risk of depression in women is greatest during the child-bearing years. Considering that about 50% of pregnancies are unplanned, women may become pregnant while on antidepressants, may have their depression or anxiety relapse during pregnancy or postpartum, or may be unwell and untreated before and during pregnancy and the postpartum period. The impact of the symptoms of depression and anxiety can cause risk to the mother and also have a negative effect on child development. This presentation is intended to assist in understanding the impact of untreated maternal depression and anxiety on fetus, neonate, child and mother; to review the effects of fetal exposure to psychotropic medications (antidepressants); and to summarize general management of perinatal mood/anxiety disorders.

Introduction

This presentation is intended to assist in understanding the impact of untreated maternal depression and anxiety on fetus, neonate, child and mother; to review the effects of fetal exposure to psychotropic medications (antidepressants); and to summarize general management of perinatal mood/anxiety disorders.The prevalence of depression in women is *twice* that in men (National Comorbidity Survey[1]) and this is consistent across types of studies and different cultures.[2] The estimated lifetime prevalence of major depression in women ranges from 9% to 26%, with the risk of depression being greatest during the child-bearing years. Considering that about 50% of pregnancies are unplanned, women may become pregnant while on antidepressants, may have their depression or anxiety relapse during pregnancy or postpartum, or may be unwell and untreated before and during pregnancy and in the postpartum period. Pregnancy does not protect women from depression: up to 70% of pregnant women express having depressive symptoms. A systematic review showed prevalence rates of 7.4%, 12.8% and 12% for first trimester (T1), T2 and T3 respectively.[3] Untreated depression/anxiety can have negative fetal/obstetrical and neonatal outcomes. The impact of the symptoms of depression and anxiety can cause risk to the mother and also have a negative effect on child development (*see* Table 1). Although studies are limited and sometimes conflicting about these effects, the impact on fetal and child development is likely significant. The mechanisms of this impact are not known. Some evidence suggests that there is an impact of maternal symptoms on infant's HPA axis and increased levels in newborns of catecholamines and cortisol.[13]

Antidepressants in Pregnancy

Many psychotropic medications are used to treat depression and/or anxiety in pregnancy. These include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), other groups of antidepressants, as well as benzodiazepines and atypical antipsychotic agents (*see* Table 2). Sertraline, fluoxetine, citalopram and paroxetine are SSRIs; from these, fluvoxamine is rarely used in pregnancy. Despite the controversies regarding risk of malformations possibly caused by paroxetine, there are some women who have not responded to medications other than Paxil, but do very well on this agent. One must evaluate the risk of changing their regimen to other medications or to try something different when they are stabilized on the drug.

TABLE 1 Untreated Depression/Anxiety

Fetal/Obstetrical Outcomes[4]	▪ Spontaneous early labour, preterm delivery ▪ Lower birth weight; fetal distress ▪ ↓ fetal growth ▪ ↑ risk for spontaneous abortion ▪ ↑ risk for pre-eclampsia ▪ ↑ risk for operative/instrumental deliveries
Neonatal Outcomes[5-8]	▪ ↑ risk for poor neonatal adaptation ▪ More likely admission to neonatal ICU ▪ Some evidence for lower Apgar scores and smaller head circumference ▪ Growth retardation, slowed mental development ▪ Excessive crying, irritability, hostility, erratic sleep
Child Development[6,7,9.10]	▪ Negative effect on maternal-fetal and maternal-infant bonding ▪ Difficulties with affect regulation, e.g., tantrums ▪ Cognitive delays, behavioural and emotional difficulties, maladaptive social interactions ▪ Display more fear and anxiety and have more insecure and disorganized attachment styles ▪ Higher rates of ADHD ▪ Higher impulsivity and lower IQ at age 14-15 years
Risk to Mother[11,12]	▪ Poor nutrition and impaired self-care ▪ Failure to follow medical and prenatal guidelines ▪ Worsening of comorbid medical illness ▪ Increased exposure to tobacco, alcohol and drugs ▪ Postpartum psychiatric complications ▪ Impact on family members

TABLE 2 Antidepressants in Pregnancy

SSRIs	FDA risk category[a]	SNRIs	FDA risk category[a]
Fluoxetine (Prozac)	**C**	**Venlafaxine (Effexor)**	**C**
Sertraline (Zoloft)	**C**		
Paroxetine (Paxil)	**D**	**Desvenlafaxine (Pristiq)**	**C**
Fluvoxamine (Luvox)	**C**	**Duloxetine (Cymbalta)**	**C**
Citalopram (Celexa)	**C**		
Escitalopram (Cipralex)	**C**		
Tricyclic Antidepressants	FDA risk category[a]	Others Antidepressants	FDA risk category[a]
Nortriptyline	**C**	**Bupropion (Wellbutrin)**	**B**
Desipramine	**C**	**Mirtazapine (Remeron)**	**C**
		Trazodone (Desyrel)	**C**

[a] Categories used by US FDA to classify drug safety during pregnancy:
A - controlled studies showing no risk; B - no evidence of risk in humans; C - risk cannot be ruled out; D - positive evidence of risk, X - contraindicated in pregnancy

Escitalopram, desvenlafaxine and duloxetine are segregated from other drugs in their class in Table 2 because they are newer and have less data regarding their use in pregnancy and resulting outcomes. Because they are new, many women become pregnant taking these medications. If they are well controlled, there is no need to change therapy, given that it is unknown whether another drug would work for the patient. On the other hand, these would not be drugs of choice to be initiated during pregnancy, unless they had previously been effective for treatment.

TABLE 3 Psychotropics in Pregnancy

Atypical Antipsychotics	FDA risk category[a]	Benzodiazepines	FDA risk category[a]
Olanzapine	**C**	**Lorazepam**	**D**
Quetiapine	**C**	**Clonazepam**	**D**
Risperidone	**C**		

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Tricyclic antidepressants (TCAs) are still used, typically nortriptylline or desipramine because they have the least anticholinergic side effects. Furthermore, women who have first trimester bleeding can be treated with these agents preferentially, to avoid exposure to SSRIs or SNRIs and the associated increased risk for bleeding. Some women respond very well to bupropion, which increases dopamine and norepinephrine, or to mirtazapine. Atypical antipsychotics may be used for sleep protection or can be effective for anxiety. Benzodiazepines, such as lorazepam, can be used for sleep as needed during pregnancy, and clonazepam when the symptoms of anxiety are so great that normal functioning is impaired while waiting for an SSRI or SNRI to start working.

But will every woman who has severe symptoms take medication? No.

In addition to studies about this issue, clinical experience shows that the reason is largely one of the stigma associated with taking medications for depression/anxiety during pregnancy. Patients will often take medications for reflux, such as ranitidine, but will not take SSRIs for severe anxiety or depression. This group of women usually perceives the notion of harm, stating, "I will not take anything to harm my baby." Some say, "I can beat this" or "I will try anything else" rather than take medication. These women's biggest concern is of the medication harming the fetus. Many women refuse to take medications for fear of poor neonatal adaptation syndrome (PNAS) or for fear of unknown neurodevelopmental outcomes in their babies. Patients often conduct their own research on the Internet, which can further increase their anxiety and exacerbate existing fears. An unsupportive partner saying "You will not make my child into a zombie" can also be a problem.

There is however a group of women who are aware they are so sick that they are consequently worried about what their condition will do to the baby. These cases are less common and these women usually have a history of severe depression/anxiety before conception, perhaps also during a previous pregnancy or postpartum period. They have good insight into their illness, remaining on medication or beginning treatment during pregnancy. With subsequent pregnancies, they often say, "I never want to feel like this again." Their partner is generally supportive.

Risks Associated with Antidepressant Use in Pregnancy

The general population baseline risk of congenital malformations is about 3%, and of cardiovascular malformations, 1%. Rates of spontaneous abortion vary in the general population between 15% and 20%. Pre-term births occur in approximately 13% of pregnancies. Neonatal outcomes, such as poor neonatal adaptation and persistent pulmonary hypertension of the newborn (PPHN) also have a baseline incidence in the general population, as do impaired developmental outcomes.

The consensus at this time is that antidepressants do not appear to increase the risk for overall congenital malformations above the 3% population baseline or above 1% for cardiovascular malformations. The consensus is based on data available prior to 2005, including data on exposure to paroxetine and other SSRIs, SNRIs, and selective dopamine reuptake inhibitors (SDRIs). Since 2005, controversies have arisen about an increased risk of major malformations after first trimester exposure. It is important to note that there are methodological flaws with many of the studies, a lack of consistency regarding major malformations found, and they do not controlled for maternal depression and anxiety. These issues relate particularly to reported malformations after exposure to paroxetine, where there may be a small (1 in 200) increase in risk for congenital and cardiovascular malformations. Nonetheless, the use of antidepressants is acceptable if maternal symptoms are severe. In cases where the patient is concerned about potential malformations, routine fetal nuchal translucency ultrasound can be done at 10-14 weeks, followed by further investigations if needed.

As for obstetrical outcomes after exposure to antidepressants, an increase in spontaneous abortion of about 4% above the study baseline (12.5% vs. 8.7%) has been reported.[14-17] This represents a relative risk (RR) of 1.45. No differences were found among antidepressant classes (SSRIs, SNRIs, TCAs, dual action antidepressants [SDRIs]). The odds ratio (OR) was calculated to be 1.7 for SSRIs and SNRIs. With these findings, the consensus remains that the use of antidepressants is acceptable in pregnancy if maternal symptoms are severe.

Recent studies have shown that antidepressant use during pregnancy is associated with a small risk for preterm birth. Data on neonates having a lower birth weight and lower Apgar scores are inconclusive. Again the consensus is that use of antidepressants for treatment of depression or anxiety during pregnancy is acceptable.

Antidepressant Effect on Neonatal Outcomes

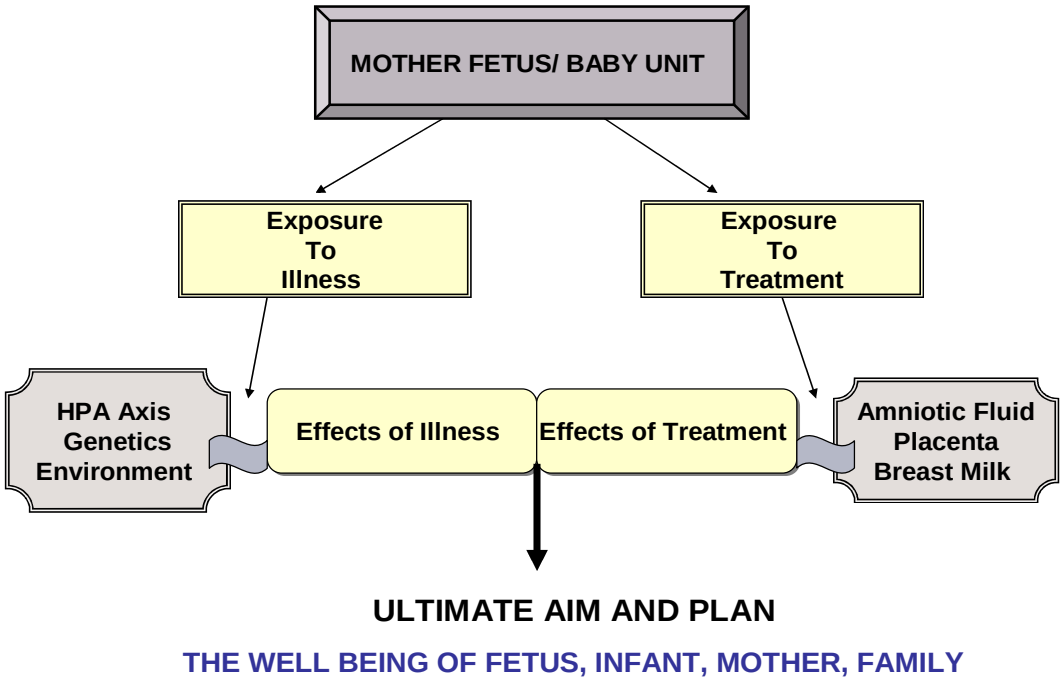
Poor neonatal adaptation syndrome (PNAS)[16-21] occurring with all antidepressants and having a risk of 4-30%, is likely a combination of serotonin toxicity and a neonatal type of discontinuation syndrome. There are probably a number of other factors at play, such as genetic predisposition and the specific receptor binding range of the antidepressant. The onset can occur immediately or a few hours after delivery, or within days of birth. Symptoms are transient and generally resolve within days, within a few weeks at the most. Common symptoms include irritability, hypertonia, tremor, jitteriness, some difficulty feeding. There is no evidence at this time for long-term neurobehavioral effects. Most infants do not require admission to a neonatal unit and can be monitored using the Neonatal Abstinence Scale (NAS); there are as yet no better scales. Infants requiring critical care usually have prominent respiratory problems or seizures. The consensus is that use of antidepressants remains acceptable and it is important to educate parents and care providers about PNAS. Frequent neonatal monitoring is required for at least three days postpartum then post-discharge follow-up with a paediatrician is recommended.

Persistent pulmonary hypertension of the newborn (PPHN), which can be a lethal condition, has been reported to occur after exposure to antidepressants. It has been proposed to be linked to exposure to SSRIs during the second part of pregnancy at 20 to 40 weeks' gestation.[22] There are not enough data or additional studies to be able to draw conclusions.

Developmental Outcomes

Prospective studies on exposure to fluoxetine and TCAs, and controlled for depression and other variables, showed no difference for children up to 7 years of age in cognitive development, mood, temperament, activity, distractibility, or behavioural problems.[23,24] These are reassuring data but they are very limited. The consensus is that it is acceptable to use antidepressants if maternal symptoms are severe.

FIG. 1 The Goal



Women with history of depression and anxiety can benefit from a *prenatal* consultation so that a flexible but comprehensive plan is in place for when they become pregnant and for the postpartum period. The prenatal and perinatal consultations are focused on risk assessment and treatment tailored to the individual. The risk/benefit assessment needs to be documented.

If symptoms are mild, psychotherapy should be considered over medication. Psychoeducation for patient and partner is important. Symptom management can be achieved through individual or group therapy, interpersonal or cognitive behavioural therapy. If medication is indicated, avoid exposing the fetus/neonate to more than one agent if possible. Because of the physiological changes during pregnancy, dose adjustment may be required if relapse is imminent. It is important to monitor for symptoms and increase dosing as needed. Choose medication based on previous personal use, pregnancy/postpartum use, and history of positive response. If drug treatment is new, then one can usually initiate with sertraline (venlafaxine, if there is severe anxiety and quicker improvement is needed). Sertraline is often chosen for its favourable profile with breastfeeding.

In summary, use of antidepressants in pregnancy is acceptable. Treatment decisions are based on the severity of maternal symptoms and on an individualized risk/benefit analysis. There must be a plan involving the patient and the partner, which covers all options for treatment and is flexible. Physicians prescribing psychotropic medications to women of child-bearing age should consider the choice of medication and how much is known about its effects during pregnancy and on child development. They should also note which form of birth control is being used as part of every evaluation for possible treatment with a psychotropic agent.

There is no such thing as non-exposure. If the mother is symptomatic, the fetus/newborn will be exposed to maternal illness (depression/anxiety) or to medication or, if the mother is not adequately treated, to both. Minimize exposure to only one: either medication or illness. If medication is used, the goal is to achieve full remission.

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