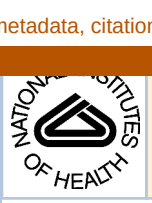

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Antidepressant Use During Pregnancy: Current Controversies and Treatment Strategies

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Abstract

The treatment of depression during pregnancy is both a common and complex clinical challenge. The decision to expose the fetus to antidepressant medication during pregnancy must be weighed against the risks of untreated maternal depression to both mother and fetus. Maternal depression during pregnancy has been associated with increased rates of preterm birth and maternal substance use. The safety of antidepressant use during pregnancy appears to be largely reassuring but there remain two areas of controversy including neonatal withdrawal syndrome and primary pulmonary hypertension of the newborn (PPHN). Individualized treatment recommendations based on the patient's history are essential in order to optimize outcomes.

Keywords

Depression; pregnancy; antidepressants; safety; PPHN; neonatal withdrawal syndrome

Introduction

Prescription drug use during pregnancy is a common phenomenon. Between 1996 and 2000, 64% of all women who delivered a child had a drug other than a vitamin or mineral supplement prescribed in the 270 days before delivery, 97% of which were not FDA Pregnancy Category A (see Table 1) (1). The choice of whether to prescribe a medication during pregnancy is a difficult one and prescribing must take into account the potential risks and benefits to the unborn infant and the mother. When the mother is diagnosed with a potentially life threatening illness, the choice of whether to prescribe a medication often becomes obvious. However, when the mother faces a illness that is not viewed as immediately life threatening, the decision to prescribe becomes more complicated. One area of controversy is the use of antidepressants during pregnancy.

There are a number of reasons why the use of antidepressants during pregnancy is controversial. Firstly, antidepressants are often considered “luxury” medications- i.e. ones that can and should be stopped during pregnancy, in the same category as ibuprofen or sleep aids. This belief stems from common misperceptions of Major Depression (MDD) and other psychiatric illnesses as different from, and not as serious as, medical illnesses. Secondly, antidepressants are often prescribed in patients that do not meet full diagnostic criteria for MDD or other psychiatric

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illness. For example, as with any medical illness, it may be appropriate to discontinue antidepressant medications during pregnancy in patients whose symptoms were subsyndromal, i.e. mild or transient,. Thirdly, discontinuation of antidepressants during pregnancy has risks. The psychiatric literature has demonstrated that exposure to untreated MDD during pregnancy can have serious adverse consequences for the developing neonate such as premature birth, low birth weight and future behavioral disturbances (Li et al 2009, Davis et al 2005). Lastly, a majority of women will relapse with MDD if their antidepressants are stopped during pregnancy significantly increasing the risk of postpartum depression (PPD) (2;3). .

This review will provide guidance regarding the complex decision making process and other issues surrounding antidepressant use during pregnancy and lactation. Common questions that arise in clinical practice will be discussed including: Which antidepressants are safer during pregnancy? What are the FDA recommendations? Should the antidepressant be tapered prior to labor and delivery? What about withdrawal symptoms or adverse outcomes for the infant?

Why use antidepressants during pregnancy?

The treatment of women with depression or other psychiatric illness during the perinatal period (pregnancy or postpartum) poses a complex clinical challenge. However, given that perinatal depression has an estimated prevalence rate of at least 10% in the general population, this challenge is routinely encountered and must be squarely addressed in order to help the patient make an informed decision (4-7). Rates of antidepressant medication during pregnancy and lactation have continued to rise in North America over the past decade (1;8;9), and antidepressant use in pregnancy is now estimated to be at least 1 in 10 women (9). The decision to use antidepressant medication during pregnancy or lactation must be weighed against the risks of untreated maternal depression and this risk/benefit ratio must be carefully discussed with each patient.

Avoiding antidepressant use during pregnancy or lactation is often not an option. Studies have shown that terminating antidepressant treatment in pregnancy in women with a previous history of depression leads to relapse of symptoms in as much as 60-70% of women (2;3). Relapse then exposes the developing infant to the effects of untreated depression, which has potentially devastating consequences for the patient, infant, and family (10;11). Antenatal depression has been associated with low maternal weight gain, increased rates of preterm birth (12), low birth weight, increased rates of cigarette, alcohol and other substance use (13), increased ambivalence about the pregnancy and overall worse health status (14). Additionally, prenatal exposure to maternal stress has been shown to have consequences for the development of infant temperament (15). Children exposed to perinatal (either during pregnancy or postpartum) maternal depression have higher cortisol levels than infants of mothers who were not depressed (16-19) and this finding continues through adolescence (19). Importantly, maternal treatment of depression during pregnancy appears to help normalize infant cortisol levels (20). These findings may partially explain the mechanism for an increased vulnerability to psychopathology in children of mothers with antenatal depression (21).

Untreated depression during pregnancy is also one of the strongest risk factors for the development of postpartum depression (PPD). One should note that PPD has potentially devastating consequences including suicide and infanticide. While the risk for suicide deaths and attempts is lower during and after pregnancy than in the general population of women, suicides account for up to 20% of all postpartum deaths and represent one of the leading causes of peripartum mortality (22). PPD has been associated with significantly increased rates of infantile colic and impaired maternal-infant bonding (23). PPD is also associated with worse parenting behavior, such as decreased rates of both infant safety and healthy child development practices (24), and increased use of harsh discipline practices (25).

While every case should be considered individually, many pregnant women with either a history of MDD or new onset MDD during pregnancy require the use of antidepressants in order to stay psychiatrically well. Since adverse outcomes for the child exposed in utero to MDD have been demonstrated, it is important to consider MDD in the mother during pregnancy an exposure for the baby. Keeping the mother psychiatrically well should be the overarching goal of treatment during pregnancy for both the mother and the child. Thus, the discontinuation of antidepressants in a pregnant or soon-to-be pregnant woman should only be done in collaboration with the patient's psychiatrist, and after a careful review of the risk/benefit ratio for both mother and baby has been assessed.

Lack of Data Regarding the Use of Antidepressants during Pregnancy

Unfortunately, there is limited evidence from research studies to guide the clinician treating women with perinatal depression. Consequently, for many women, the decision making process to either initiate or continue to use psychotropic medications during pregnancy or lactation becomes highly stressful and emotionally painful. The woman often faces misconceptions and incorrect information from well-intentioned family, friends and care providers (26). Thus, although having a baby is supposed to be a time of great joy in a woman's life, suffering from mental illness during pregnancy or postpartum can quickly become a nightmare.

Multiple barriers exist that have compromised the accumulation of reliable data on the use of antidepressants during the perinatal time. These barriers include ethical challenges, such as the inability to randomly assign depressed pregnant women in clinical trials, practical challenges, such as multiple confounding variables in observational cohort studies, as well as the lack of an adequate comparison group in most studies which makes it difficult to determine the role of underlying depressive illness versus antidepressant use on fetal outcomes (27;28). Thus, the evidence base regarding the safety of antidepressant medication during pregnancy and lactation has many holes and unanswered questions such as:

- What are the short and long term risks to the fetus of antidepressant exposure during pregnancy?
- What is the risk to the fetus of untreated maternal depression during pregnancy?
- What are the risks of either antidepressant exposure or untreated depression to neonates during lactation?

Despite these unanswered questions and lack of data, the clinician must help his or her patient make appropriate clinical choices regarding antidepressant use during pregnancy, weighing both the potential risks of untreated depression as well at the potential risks of antidepressant use. What information is currently available to help guide physicians advice to their pregnant patients?

FDA Guidelines

Since 1979, the Federal Drug Administration (FDA) has required that pharmaceutical product information include information about safety during pregnancy (29). In addition, products are classified under one of five letter categories (Table 1). Until recently, this information has been based largely upon animal studies. Indeed, the well-known FDA pregnancy category system (Table 1) uses evidence from animal studies as part of the definitions of 3 out of the 5 categories. However, the categories are confusing and imply an increasing level of risk from category A to category X which is not, in fact, the case. For example, oral contraceptives are in category X simply because there is no reason to use them in pregnancy, not because there is evidence of birth defects if they are used during pregnancy. Further, the level of investigation used to

categorize individual medications varies from medication to medication as does the level of risk actually imposed by a particular drug. Medications may be placed in the same category and have vastly different levels of risk and/or different levels of evidence supporting their categorization (see Table 1). The FDA Pregnancy Categories therefore can provide a "quick and dirty" assessment but may not provide information that is useful in planning clinical care.

In 1997 the FDA Pregnancy Labeling Task Force was formed to revise the pregnancy category system with the goal of improving the ability of the FDA system to help clinicians make informed clinical decisions when prescribing medications to pregnant women. (30). This Task Force has investigated the following issues:1) the FDA categories do not address dosing; 2) lack of consideration of time of exposure to the medication; and 3) excessive reliance on animal data and lack of human data. In March of 2000 a FDA subcommittee proposed a new model for pharmaceutical labeling which in May 2008 became a FDA "Proposed Rule," meaning that the new model is currently being considered and comments on the rule have been solicited. It is likely that the model will become effective on or about June 30, 2010. This new model eliminates the previously established categories and instead will provide information and summary data on both clinical considerations and risk assessment for fertility, pregnancy and lactation (30). This system attempts to include all currently available information in order to help the clinician weigh the risks and benefits of prescribing a drug during pregnancy. While providing more information to the clinician than the Category system, this approach can also be confusing to the clinician making a risk-benefit analysis who does not have much experience with a particular drug.

FDA "Black Box" Warnings and Public Health Advisors for Antidepressants and Pregnancy

"Black Box" warnings are generally placed on the label of a medication when the FDA judges that a potential side effect or complication is serious enough to warrant drawing the clinician's attention to it immediately. A Public Health Advisory is a statement issued by the FDA concerning a particular issue with an individual or class of medications (or food) that summarizes all currently available information on the topic. Public Health Advisories are generally issued when there is concerning information, but does not necessarily give specific recommendations.

To date there is one "Black Box" warning regarding the use of a particular class of antidepressants, serotonin reuptake inhibitors (SSRI's) and their possible association with an increased risk for Persistent Pulmonary Hypertension (PPHN). We will review the literature on risks associated with the SSRI's and other antidepressant medications below. In addition, the FDA has also issued a Public Health Advisory entitled, "Treatment Challenges of Depression in Pregnancy and the Possibility of Persistent Pulmonary Hypertension in Newborns," which includes information on the potential risk of relapse when women discontinue their antidepressants for pregnancy and, in addition, summarizes the available data known regarding not only PPHN but the risk of withdrawal symptoms in the newborn exposed to antidepressants in utero.

Potential Risks to the Fetus Associated with Antidepressant Use During Pregnancy

Persistent Pulmonary Hypertension

PPHN is a failure of the pulmonary vasculature to decrease resistance at birth. This results in significant breathing difficulties for the infant, hypoxia, and usually leads to intubation. It has about a 10-20% mortality rate and also results in significant morbidity (31). It is a very rare

condition, affecting 1-2 infants out of 1000 in the general population (32;33). PPHN has been associated with a number of factors including, maternal smoking (34), maternal diabetes, sepsis, meconium aspiration, and C-section, among others (33).

To date there have been three relatively large studies on the association between SSRI's and Persistent Pulmonary Hypertension (PPHN) in the newborn with conflicting results. The first was published in 2006 (35) and is the basis for the FDA Alert issued in July 2006 regarding the possible association of PPHN with SSRI antidepressants. This case-control study compared 377 women who had infants diagnosed with PPHN to 836 matched control women with infants not diagnosed with PPHN. 14 of the infants with PPHN had been exposed to an SSRI after the 20^{th} week of gestation compared to 6 infants who did not have PPHN (35). This generated an adjusted (for maternal diabetes, race, body-mass index) odds ratio of 6.1. A second study, was conducted through the Swedish Medical Birth Register for the years 1997-2005 and examined 831,324 women who had given birth during this time (36). Antidepressant use was identified at the first antenatal care visit (usually first trimester) and through prescriptions written by the antenatal health service. This method did not include prescriptions written by other physicians such as psychiatrists, and thus information on antidepressant use late in pregnancy was not complete. Of 506 infants with PPHN, 11 had been exposed early in pregnancy to an SSRI which generated a relative risk estimate of 2.01 (CI 1.00-3.60). When only those cases that had a known exposure late in pregnancy and were born at or after 37 weeks were included the relative risk rose to 3.70 (CI 1.01-9.48) (36). The most recent study used data from the HMO Research Network Center for Education and Research on Therapeutics from 1996-2000 (37). 1104 infants exposed to SSRI's during the third trimester were compared to a matched sample of 1104 infants not exposed to SSRI's. 5 infants, 2 from the exposed group and 3 from the nonexposed group, were identified with PPHN. There was no difference in prevalence rates between the two groups (37).

One issue that complicates interpretation of these studies is that several factors that are associated with the development of PPHN in the general population, including maternal smoking, maternal diabetes, and high pre-pregnancy BMI are also associated with MDD and psychiatric disorders in general. Future, prospective studies that control for such factors are needed in order to fully elucidate the association between SSRI's and the development of PPHN in the newborn. It is also important to keep the potential elevated risk in perspective by considering the absolute risk. PPHN is an extremely rare condition, occurring in 1-2 infants out of 1000 in the general population (32;33). If one assumes that SSRI's increase the odds of the development of PPHN 6 times the rate in the general population, only 6-12 (0.6-1.2%) infants exposed to SSRI's will develop PPHN out of 1000 exposed. Thus, approximately 99% of women who take SSRI's during pregnancy will give birth to a healthy infant who does not develop PPHN. In contrast, the risks associated with untreated depression during pregnancy are much higher and more common.

Withdrawal Symptoms

The first report of withdrawal symptoms in babies exposed to antidepressants occurred in 1973 (38). It is unclear if “neonatal withdrawal syndrome” is actually a result of withdrawal from the antidepressant medication or is due to a toxicity mechanism. Thus, an alternative term such as “poor neonatal adaptation”, or “neonatal neurobehavioral syndrome” may be a better description. There are a number of limitations in the available literature in this area, including inconsistent definitions, no tool available to evaluate for the presence or absence of the syndrome (for instance if an exposed infant has only constant crying does that meet the criteria for the syndrome?), a lack of blinded ratings and a lack of studies regarding possible treatment or prevention of the syndrome. Regardless, the FDA instituted a class labeling change in 2004 for both SSRI and SNRI (serotonin-norepinephrine reuptake inhibitors) antidepressants

warning that third trimester exposure to antidepressants may be associated with signs and symptoms consistent with the syndrome. According to the label change, “reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying.” The subsequent result has been that many practitioners have recommended tapering antidepressants prior to labor and delivery even though it remains unclear if this decreases the risk for the syndrome and if this practice increases the risk for PPD. Furthermore, most cases of the neonatal syndrome appear to be very mild, self-limited and do not appear to be associated with lasting repercussions (39). Additionally, other confounding factors and unanswered questions further complicate the picture including: 1) what effect breastfeeding may have on the risk for the syndrome, and 2) minimal characterization of maternal psychiatric illness and 3) use of multiple psychotropic agents during pregnancy. (39). For example, available data suggests that approximately 1/3 of exposed infants will have at least mild symptoms consistent with the syndrome and that this risk increases when multiple agents, particularly benzodiazepines, are used (40). Clearly, larger, more rigorous studies of the syndrome as well as strategies to minimize the rate of the syndrome are needed. However, at this time there is simply not enough evidence from a safety perspective to recommend tapering of antidepressants in the third trimester, particularly in cases of moderate to severe maternal mental illness.

Antidepressants and Pregnancy: Specific Agents

Table 2 describes the currently available data on the use of specific antidepressant medications during pregnancy and lactation. Overall, with one exception (paroxetine), there does not appear to be an increased risk of major malformations with exposure to antidepressants in utero, though for many agents there is little to no data available. In general, many practitioners will prescribe SSRI medications during pregnancy since they are well-tolerated. Of the SSRI medications, both fluoxetine and sertraline have more data regarding safety than the newer SSRI's such as escitalopram. First trimester exposure to paroxetine has been associated with cardiac defects and should therefore only be used if there are no other choices for that particular patient (REF). The older tricyclic antidepressants should also be considered for use during pregnancy though side effects, particularly constipation and orthostatic hypotension may be exacerbated by pregnancy. There is limited data on the use of SNRI's, , bupropion, mitazapine and monoamine oxidase inhibitors, though any of these agents may be appropriate in a particular patient.

Recommendations Regarding the Clinical Care of Women with MDD During Pregnancy

Because of the limited evidence base, pregnant or lactating women who use antidepressant medication often receive conflicting information regarding the safety of treatment. The decision to use antidepressant medication in a woman with MDD during pregnancy or lactation needs to be made on a case by case basis taking into account the following factors: 1) past history and severity of MDD before pregnancy; 2) prior history of perinatal depression (during pregnancy or postpartum); 3) past treatment history including both psychotropics and psychotherapy; 4) current depressive symptoms and the degree to which they are interfering with the patients ability to function; 5) suicidal or psychotic symptoms that should be considered a psychiatric emergency; and finally 6) the patient's as well as the partner's (if possible) wishes for medication use during pregnancy. Every case is different and ultimately there are no hard and fast rules. Measurement of severity of depressive symptoms may be quickly accomplished using a screening instrument for perinatal depression such as the Edinburgh Scale (41), and can help the busy obstetrical provider make a rapid assessment.

Ideally, a collaborative and multidisciplinary treatment approach that includes the patient's psychiatrist, obstetrician, and pediatrician is critically important. This collaborative approach provides the best opportunity to:

- Individualize treatment based on the severity and history of the mother's illness
- Appropriately educate the patient about the potential risks and benefits of treatment versus no treatment and side effects for mother and baby
- Avoid communicating “mixed messages” to the patient about the risk and benefits of treatment
- Institute a universal screening protocol for perinatal depression
- De-stigmatize perinatal depression
- Ensure the mental and physical health of mother and baby and family

The ideal situation is to begin planning for pregnancy *prior* to pregnancy. It is important to assume that every woman of childbearing age will get pregnant and to discuss medication use during pregnancy and use of birth control measures as part of their ongoing treatment. If a woman is taking a medication that should clearly *not* be used during pregnancy a discussion should be held with the woman and, if possible, her partner to discuss this fact and to plan what should be done in event of accidental pregnancy. As many as 50% of pregnancies are unplanned in the U.S. (42); this fact highlights the importance of assuming that all women of reproductive age may become pregnant, and developing appropriate treatment and contingency plans aimed at minimizing the chance that necessary psychiatric medications will be abruptly discontinued and the patient will relapse.

The patient's past psychiatric history, severity of symptoms and medication response history all play a significant role in designing a course of clinical care during pregnancy. For example, while Prozac and Zoloft are often considered appropriate antidepressant choices during pregnancy, if a woman has a history of not responding to either of these medications they cannot be part of the treatment plan. Severity of illness is important to take into account: a case in which the symptoms of depression were mild, responded well to medication and had not recurred could be considered for discontinuation of the medication prior to pregnancy. In contrast, a case in which depression was severe, dangerous and required hospitalization several times would not be a candidate for medication discontinuation.

At the same time, the patient and her partner's wishes regarding medication use during pregnancy should be taken into account when designing a treatment plan. If one or the other is strongly against medication use during pregnancy it is best for the treatment provider to make sure they understand the risks of no treatment to both the mother and the baby, the rates of relapse, and to outline a course of close follow-up during and after pregnancy rather than insist on the use of medication during pregnancy. A partnership with good communication with the patient and her partner, as well as the treating psychiatrist, is important to maintain so that if there *is* a relapse of illness the patient will remain safe and is more likely to seek care and treatment.

While each case is individual and there are no hard and fast rules there ARE some “rules of thumb” that can be used when designing a treatment strategy (See Table 3):

1. All medication changes should be done prior to pregnancy if possible. This minimizes the number of exposures to the baby and promotes mood stability for the mother.
2. Ideally the patient should be stable psychiatrically for at least 3 months before attempting pregnancy. This is not always practical but should provide some evidence and reassurance that the patient's mood is stable prior to entering pregnancy.

3. Use medications that we know something about: Older is usually better. If a medication has been available for awhile there is at least some evidence that it is unlikely to be associated with major organ malformations. See Table 2 for a description of what is currently known about various antidepressants.

4. *Minimize the number of exposures for the baby*. Try to minimize the number of medications used but also consider exposure to psychiatric illness an exposure. Changing medications for breastfeeding increases the number of exposures. One common scenario is for a woman on a newer antidepressant to become pregnant and then to receive the recommendation to switch antidepressants to an older medication that has more evidence for safety during pregnancy. While this might have made sense prior to pregnancy, this plan would actually increase the exposures for the baby. First the baby has already been exposed to the newer antidepressant and switching to a second medication would be another exposure. In addition, the likelihood that the patient would relapse while switching is high, thus exposure to the mood disorder would be a third exposure for the child.

5. *Consider breastfeeding when planning for pregnancy*. Consider whether the medication should be used during breastfeeding and what the plan would be for monitoring the medication during breastfeeding.

6. If a baby was exposed to a medication during pregnancy, it may not make sense to discontinue the medication (or alternatively not breastfeed) for breastfeeding. The baby experienced a larger concentration of the drug in utero compared to the concentration that will be found in breastmilk. That being said there are certain medications that might be more difficult to justify continued exposure during breastfeeding.

Conclusions

Antidepressant use during pregnancy is often necessary in order to prevent maternal psychiatric illness. Discontinuation of antidepressants during or shortly before pregnancy has been associated with a high rate of relapse resulting in exposure to maternal depression for the neonate. Such exposure is not benign and has been associated with poor outcomes for both the baby as well as the mother and may, in fact, have long-term consequences. Individualized recommendations based on the patient's past history and medication regimen should ideally be implemented prior to pregnancy with a goal of minimizing exposures for the baby, including to maternal psychiatric illness. Future research in the area of perinatal psychiatry will hopefully address many of the gaps in the literature including, for example, the safety of antidepressant use during pregnancy and lactation, long-term outcomes for exposed children, consequences of exposure to maternal illness, and whether antidepressants should be tapered prior to delivery. While knowledge gaps exist and the data is limited in scope, the overall safety of antidepressant use during pregnancy currently appears to be good with only one antidepressant associated with major malformations. The association of SSRI antidepressants with an increased risk of persistent pulmonary hypertension has been demonstrated in two studies, though a recent third did not support the association. Despite the possible association, the absolute risk remains small with less than 1% of exposed infants developing the syndrome. Neonatal withdrawal syndrome remains an active area of controversy though interpretation of the literature is compromised by the lack of a specific definition of the syndrome, specific measurement tools, controls for severity of maternal illness, and blinded studies. In all cases, utilizing strategies such as planning for pregnancy, educating the mother and family regarding the risks and benefits of treatment as well as the potential risks of no treatment, and using a team approach will optimize outcomes for both mother and child.

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Table 1

FDA Pregnancy Categories

FDA Category	Description	Problems
A	Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities.	
B	Animal studies have revealed no evidence of harm to the fetus, however, there are no adequate and well-controlled studies in pregnant women. **or** Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.	Not all drugs in this category have the same level of investigation. For example bupropion was originally classified in this category because of one small sample of women. It has since been reclassified at Category C based on animal studies.
C	Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women. **or** No animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.	Not all drugs in this category have the same level of risk. For example, simethicone which is not absorbed systemically and therefore is no risk to the fetus and carbamazapine which is known teratogen are both in this category (Frederiksen)
D	Studies, adequate well-controlled or observational, in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk.	
X	Studies, adequate well-controlled or observational, in animals or pregnant women have demonstrated positive evidence of fetal abnormalities. The use of the product is contraindicated in women who are or may become pregnant.	Some drugs are placed in this category because there is no reason to use them during pregnancy, not because of evidence of fetal abnormalities. Example: Oral Contraceptives

Table 2

Summary of Antidepressant Medications During Pregnancy and Lactation

Medication	Dosing Range	Potential adverse event(s): Pregnancy	Potential adverse event(s): Lactation
Selective serotonin reuptake inhibitors			
Sertraline	25mg-200mg	No confirmed evidence of birth defects in 1st trimester exposure. Risk of SSRI withdrawal syndrome with 3rd trimester exposure. (43)	Minimal detection of drug in infants serum. (44; 45)
Paroxetine	10mg-50 mg	Small absolute increased risk of cardiac defects in 1st trimester exposure (no more than 2 per 1000 births). Risk of SSRI withdrawal syndrome with 3rd trimester exposure.(43)	Minimal detection of drug in infants serum. (44; 45)
Citalopram	10mg-60 mg	No confirmed evidence of birth defects in 1st trimester exposure. Risk of SSRI withdrawal syndrome with 3rd trimester exposure.(43)	high milk/plasma concentration at higher doses. (45)
Fluoxetine	10mg-60mg	No confirmed evidence of birth defects in 1st trimester exposure. Risk of SSRI withdrawal syndrome with 3rd trimester exposure. (43)	Long half-life can increase the potential for accumulation. (45)
Escitalopram	10mg-20mg	No confirmed evidence of birth defects in 1st trimester exposure. Risk of SSRI withdrawal syndrome with 3rd trimester exposure.(43)	Very limited data to date shows lower milk/ plasma concentrations as compared to citalopram. (46)
Tricyclics			
Desipramine	25mg-200mg	No confirmed evidence of birth defects in 1st trimester exposure. Risk of SSRI withdrawal syndrome with 3rd trimester exposure.(43)	Minimal detection of drug in infants serum. (44; 47)
Imipramine	25mg-200mg	No confirmed evidence of birth defects in 1st trimester exposure. Risk of SSRI withdrawal syndrome with 3rd trimester exposure.(43)	Minimal detection of drug in infants serum. (44; 47)
Nortriptyline	25mg-150mg	No confirmed evidence of birth defects in 1st trimester exposure. Risk of SSRI withdrawal syndrome with 3rd trimester exposure.(43)	Minimal detection of drug in infants serum. (44; 47)
Other Antidepressants (SNRI's and others)			
Mirtazepine	7.5mg-45mg	Limited data available; no confirmed evidence of birth defects in 1st trimester exposure.(43)	Limited data available. Well tolerated in small study. Always monitor for changes in sleep and eating behaviors. (48)
Buproprion	75g-300mg	Limited data available; no confirmed evidence of birth defects in 1st trimester exposure.(43)	Limited data available. Small increased risk of infant seizure (case report). (49)
Venlafaxine	37.5-225mg	Limited data available; no confirmed evidence of birth defects in 1st trimester exposure.(43)	Inadequate data available
Duloxetine	20-90mg	Inadequate data available.(43)	Inadequate data available
MAOI's			
phenelzine	15-75mg	Very limited data available; no confirmed evidence of birth defects with 1st trimester exposure. (50)	Inadequate data available

Table 3

Clinical Guidelines for Treatment of Depression During Pregnancy

Clinical Pearls
• Assume all reproductive age women will get pregnant and plan ahead
• All medication changes should be done prior to pregnancy if possible
• Ideally the patient should be stable psychiatrically for at least 3 months before attempting pregnancy
• Limit the number of exposures for the baby; Consider active depression in the mother an exposure
• Use medications that we know more about:- older generally means better
• Consider breastfeeding when planning for pregnancy
• If a baby was exposed to a medication during pregnancy, it may not make sense to discontinue the medication (or alternatively not breastfeed) for breastfeeding
• Every case is unique- there are no rules
• Use a team approach