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Are Antidepressants Safe during Pregnancy & Breastfeeding?

~12% of women experience depression and 13% experience anxiety peri-pregnancy.[33] The decision on how to treat depression and/or anxiety during and after pregnancy requires careful consideration of benefits and harms and collaborative discussions with the patient.

SUMMARY OF KEY POINTS:

- Consider the potential harm to mother and baby if depression is not treated.
- Consider cognitive behavioural therapy and interpersonal psychotherapy for patients with **less severe** depression.
- Consider using an antidepressant for patients with a history of **severe** depression. Most SSRIs are considered safe during pregnancy and lactation (sertraline, escitalopram, citalopram) [CANMAT 2016].
- In females with recurrent depression who stop their antidepressant during pregnancy the rate of relapse is ~25-50%. Discuss and individualize antidepressant management depending on previous and current mental health status.

Should antidepressants be discontinued before or during pregnancy? [1,2,23,34,35]

- The decision depends on the patient's previous and current mental health status.
- Patients may be a candidate for tapering and discontinuing their antidepressant if they have had **mild or no symptoms** for ≥6 months. **Taper**: ↓ dose by 25% every 1-2 weeks. Work with patient & family to monitor closely for signs of relapse & withdrawal symptoms.
- Patients should **not** discontinue their antidepressant if they have a history of severe recurrent depression, psychosis, bipolar illness, suicide attempt, or other psychiatric comorbidities requiring drug therapy. In such patients, the harm of not taking an antidepressant may exceed the harm of taking drug therapy.
- The rate of relapse is high during pregnancy. Based on three cohort studies, discontinuation led to a relapse of depression and re-initiation of antidepressant therapy in 22%-57% of women.[23,34,35]

Is there any harm in not treating depression and/or anxiety during pregnancy & postpartum? [1,3,4,5,6,7,8,9,10,11]

- Untreated depression and/or anxiety can put the mother & fetus/baby at risk, with suicide & infanticide being a primary concern.
- Mothers with depression are more likely to miss prenatal appointments, be malnourished, engage in harmful behaviours e.g. smoking and are less likely to take prenatal vitamins. Postpartum depression can impact their ability to care for and bond with their child.
- In untreated depression, there is a higher risk of spontaneous abortions, miscarriages, gestational hypertension, preeclampsia, preterm deliveries, low birth weight, small for gestational age, cesarean section, low Apgar scores, need for neonatal intensive care, and ↑ length of hospital stay[1,5,9]. Some antidepressant studies in pregnant women have found these same risks, but most were unable to control for underlying depression.[1]
- Infants born to untreated women are at a higher risk of irritability, inactivity, and fewer facial expressions. Cognitive, emotional, and behavioural concerns can surface when an infant is exposed to a chronically depressed mother.

What is the role for non-pharmacological therapies during pregnancy? [1,4,6,7,31,37,38]

- Non-pharmacological therapies have the same role in patients with depression whether pregnant or not. Non-pharmacological therapies may be considered first line in less severe depression/anxiety and as an adjunct in **more severe** depression/anxiety.
- See RxFiles Depression Newsletter, pg 10.
- Note: electroconvulsive therapy (ECT) is considered safe & effective during pregnancy for patients with severe, refractory depression.

When should antidepressants be considered? [1,3,4,31]

- Antidepressants can be used for more **severe** depression and/or anxiety, with or without psychotherapy.
- In **less severe** depression/anxiety, antidepressants may be tried if: psychotherapy is not available or has previously failed, the patient prefers pharmacotherapy, the patient has a history of severe depression/anxiety, or has had a good response to previous antidepressants.

Which antidepressants are considered the safest during pregnancy? [1,3,4,6,12,13,14]

- Antidepressants do not appear to significantly ↑ the risk of congenital malformations more than the general population risk of 2-4%.
- Most SSRIs are considered safe. Sertraline, escitalopram, & citalopram may be preferred due to efficacy and safety profile.[CANMAT 2016] See below for specific concerns with paroxetine and ?fluoxetine; most SSRIs appear to have a similar safety profile.
- Tricyclic antidepressants (TCAs) do not appear to be teratogenic and serum levels can be monitored; however, anticholinergic side effects & risk of overdose need to be considered. Amitriptyline and nortriptyline are preferred TCAs.
- Newer antidepressants (e.g. levomilnacipran, vortioxetine, vilazodone) do not appear to be teratogenic, but there is limited data available.

Abbreviations: **SSRI**=selective serotonin reuptake inhibitor **TCA**=Tricyclic antidepressants **CANMAT**=Canadian Network for Mood and Anxiety Treatments **CPS**=Canadian Pediatric Society **ECT**=electroconvulsive therapy **PPHN**=persistent pulmonary hypertension of the newborn

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Are paroxetine and fluoxetine associated with congenital malformations? [1,2,4,6,8,15,26,36]

- Available evidence is inconsistent and has study limitations. A meta-analysis published in 2013 found the following:[26]
  - N=7, n=1,639,065: increased risk of cardiovascular malformation with paroxetine RR 1.43 (95% CI 1.08-1.88)
  - N=7, n=1,901,183: increased risk of congenital malformations with fluoxetine RR 1.25 (95% CI 1.03-1.51); however, significance varied based on analysis.
- If starting an antidepressant in a woman of childbearing potential or who is pregnant – possibly consider selecting an antidepressant other than paroxetine or fluoxetine, unless the patient has responded to either agent in the past, has failed other agents, &/or has other indications for paroxetine or fluoxetine.
- If a pregnant woman is stabilized on paroxetine or fluoxetine – often continue treatment, especially if the patient has previously failed other antidepressants. Decreasing the dose may help reduce potential risks. Switching to another antidepressant in the first trimester is an option, but switching may result in risk of relapse.

Are SSRIs associated with persistent pulmonary hypertension of the newborn? [1,3,8,16,17,18,24,27,31,32]

- The available data (case-control or cohort) is conflicting and has several limitations. If a true association exists, the risk is very small.
- Persistent pulmonary hypertension of the newborn (PPHN) is a rare but serious complication. There are several causes, including meconium aspiration 40% of cases, smoking, obesity, cesarean section, and preterm delivery, to name a few.
  - Depression itself has been linked to increased risk of cesarean section and preterm delivery.
  - PPHN has not been linked to non-SSRI antidepressants.
- There is conflicting evidence regarding the association of SSRIs and PPHN. One systematic review and meta-analysis found an absolute risk of 2.9-3.5 per 1000 births compared to the general population risk of 2 per 1000 births.[27]

Are antidepressants associated with neonatal behavioural syndrome? [1,3,4,7,8,10,19,24] (neonatal adaptation syndrome)

- Neonatal behavioural syndrome has been reported in up to 30% of infants exposed to antidepressants near term. All antidepressants carry this risk; however, it is usually mild and transient.
- Signs and symptoms include tachypnea, cyanosis, jitteriness, tremors, increased muscle tone, feeding disturbances, irritability, temperature instability, hypoglycemia, and, rarely, seizures.
- Usually presents within hours of birth, is mild, and often resolves within two weeks.
- It is not known if it results from neonatal withdrawal or toxicity. In utero nicotine exposure can cause similar symptoms.
- No specific monitoring is recommended.[CPS] Families should be counselled to observe for the above signs & symptoms.

Which antidepressants are considered safe during breastfeeding? [3,6,9,20,21,24,31]

- Postpartum use of any antidepressant is not a contraindication to breastfeeding.[CPS 2021,CANMAT 2016]
- **SSRIs** have the most safety data during lactation and are considered to have a better safety profile than TCAs. Some SSRIs may be preferred e.g. sertraline, citalopram, escitalopram.[CANMAT 2016]
- All SSRIs are excreted into breast milk to varying degrees (all less than 10%, which is considered generally safe):
  - Sertraline, paroxetine, and fluvoxamine have the lowest degree of excretion into breast milk.
  - Citalopram, escitalopram, and fluoxetine have longer t½, higher infant doses & greater number of reported infant adverse events.
- TCAs: nortriptyline, amitriptyline, & clomipramine are likely safe during breastfeeding.
- Newer antidepressants (e.g. levomilnacipran, vortioxetine, vilazodone) have limited data to establish safety during lactation.
- Educate mothers to monitor for & report sedation, nausea, reduced suckling, or any other sign of drug toxicity in the infant.

Depression screening considerations in pregnancy & postpartum [6,7,8,22,24]

- **When should patients be screened for peri-pregnancy depression?**
  - Pre-conception: ask about personal and family history of mental health disorders and treatment.
  - Pregnancy: during the first routine antenatal visit.
  - Postpartum: during routine postnatal visits at 4-6 weeks and 3-4 months postpartum.
  - Anytime throughout the antenatal & postnatal period if concerned about their mental health.

  Which depression screening tools should be used? *(in conjunction with clinical symptoms and history)*
  - Edinburgh Postnatal Depression Scale – validated for use during both pregnancy and postpartum
  - Patient Health Questionnaire 9 (PHQ-9)
  - Screening tools do not confirm a diagnosis of depression, but rather identify patients who require further assessment.
- **Avoid** using screening tools which focus on somatic symptoms (e.g. Beck Depression Inventory) as it can be difficult to distinguish between symptoms of depression versus pregnancy.[expert opinion]

Note: Canadian Task Force recommends against routine screening in peri-partum period, benefit vs cost uncertain. However, regularly assessing mental health status and overall well-being in the peri-partum period is important.[40, 41]

What are other important considerations in the management of depression & anxiety during pregnancy? [1,3,4]

- Antidepressants may be metabolized more quickly in the 3rd trimester. Increase the dose if needed, but use the lowest effective dose and readjust the postpartum dose as needed or required.
- Monotherapy is preferred over combination therapy.
- Counsel patients on the risks of stopping antidepressants abruptly.
- Avoid regular benzodiazepine use for anxiety. 1st trimester use linked to oral cleft malformations. 3rd trimester use linked to "floppy baby" syndrome (hypotonia, lethargy, sucking difficulties) & withdrawal syndrome (tremors, irritability, hypertonicity, diarrhea, vomiting, vigorous sucking).

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RxFiles Q&A Are Antidepressants Safe during Pregnancy & Lactation Extras:

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