Pharmacology of Peripartum Depression, Anxiety, and Insomnia: An Evidence-Based Review

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Goals and Objectives

Upon completion, participants will be able to:

- Understand the specific impacts of mental health on pregnancy
- List indications and safety of pharmacologic treatment for anxiety, depression, insomnia in pregnancy and postpartum
- Discuss risks and benefits of pharmacologic treatment with patients

Impact of Peripartum Depression

- Prevalence of peripartum depression is about 1 in 7 women
- Estimates range from 6.5% - 19.2%
- Pre-pregnancy depression
  - High rate of relapse if stop medications
  - 68% (vs. 26% if continue antidepressant)

Consequences of Untreated Depression

Maternal
- Poor prenatal care
- Substance use
- Poor nutrition
- High-risk sexual behavior

Neonatal/Pediatric
- Premature birth
- Low birth weight, small for gestational age
- Perinatal neonatal care, bonding, and safety concerns
- Other fetal programming
- Pediatric depression and other psychiatric disorders

Clinical Take Home Point

Untreated peripartum mental health has consequences for mom and baby (SORT B) so we need to be able to assess the risks and benefits of pharmacotherapy (but the answers are not always clear)
Peripartum Depression

Defining Depression

- **Baby Blues**: Emotional lability, irritability, sadness, and/or anxiety that peaks 2-5 days after birth and starts to resolve spontaneously by 2 weeks.

- **Perinatal Depression**: Major or minor depressive episodes that occur during pregnancy or within 12 months of delivery (vs. DSM-5 which defines it within 4 weeks).

- **Postpartum Psychosis**: Hallucinations, delusions, or bizarre behavior along with mood changes; rapid deterioration; psychiatric emergency.

Clinical Take Home Point

It may be difficult to distinguish postpartum depression from baby blues initially so you should use a validated screening tool and see patients in follow-up (SORT B).

Depression Screening

ACOG Recommendations

- Screen for depression with validated tool once in perinatal period.
- 4th Trimester - see patients by 3 weeks for brief visit, provide ongoing care as appropriate, do comprehensive visit by 12 weeks.

Screen for Bipolar

"Have you ever had periods of at least 3 days straight of feeling so happy or energetic that your friends told you that you were talking too fast or that you were too hyper?"

Depression Screening

Edinburgh Postnatal Depression Screen

Validated for prenatal & postpartum use:

- Eliminates questions on PHQ-9 that are common physiologic findings in pregnancy.
- Score >10 considered positive.
- Question #10 - thoughts of harming self.

https://the-periscope-project.org/provider-toolkit/
Peripartum Depression Treatment

- Baby Blues – Self-limited but can benefit from support groups
- Peripartum Depression – Therapy and medications depending on severity
  - Mild = group support
  - Moderate = therapy (or meds)
  - Severe = therapy and meds
- Bipolar – therapy and medications, sleep hygiene, inpatient management depending on severity
- Psychosis – emergency requiring inpatient management


Psychopharmacology for Depression

Maternal Antidepressant Use & Psych Disorders in Offspring

Large Danish cohort study showed increased risk of psychiatric disorders in children of mothers who continued antidepressants during pregnancy vs those who discontinued (HR 1.27)
- Highest risk if mothers used SSRI + other antidepressant
- Mood disorders most common psych disorders (HR 2.76)
- Population attributable fraction: 0.5% of psych disorders could be prevented if mothers had not taken antidepressants during pregnancy

Likely confounding factor was severity of maternal depression


Clinical Take Home Point

It is difficult to sort out the underlying etiology of pediatric depression and other pediatric psychiatric disorders (SORT B)

Attention Deficit Hyperactivity Disorder (ADHD)

ADHD affects 5-7% of school-age children
3 recent meta-analytic systematic reviews
- Increased risk (RR 1.2-1.6) of ADHD in child with prenatal antidepressant exposure
- Likely related to maternal psychiatric disorder rather than antidepressant
  - Exposure vs maternal psych disorder without exposure = no difference
  - Maternal psych disorder without exposure vs no exposure = RR 1.3
  - Siblings matched, one exposed and other not exposed = no difference

Figueroa et al: bupropion use associated with increased risk of ADHD (OR 3.63), but did not control for any confounders or compare to untreated depression


Clinical Take Home Point

Antidepressants do not appear to increase the risk of ADHD in offspring compared to untreated maternal depression (SORT A) with the possible exception of bupropion (SORT C)
Autism Spectrum Disorders (ASD)

ASD affects ~1% of children, typically diagnosed around age 2-3.

Systematic reviews in 2015-2016 suggest an increased risk of ASD in children exposed to SSRIs in utero.

- Case-control studies demonstrate increased risk.
- Conflicting evidence between first trimester vs later trimester exposure.
- Two Danish cohort studies using same database have conflicting results, depending on exclusion criteria.
- Newer systematic reviews and meta-analyses (2017-present) suggest confounding factors may be responsible for apparent increased risk.

- Maternal psychiatric disorders.
- Frequent exposure to healthcare may lead to more prompt diagnosis.

Clinical Take Home Point

An increased risk of ASD in offspring of mothers treated with SSRIs may be confounded by untreated maternal depression as data is conflicting (SORT B).

Neurodevelopmental Outcomes

No difference if exposed prenatally to SSRIs or untreated maternal depression:

- Intellectual disability (clinical diagnosis).
- Nonverbal cognition (non-verbal IQ at age 6).

Increased risk if untreated maternal depression, compared to maternal SSRI use:

- Overall behavioral problems (parent-reported questionnaire of 25 psychological attributes, age 7).

Motor Development

Possible small increased risk for motor delay in children exposed to antidepressants:

- Increased risk if studies relied on subjectively reported categorical data.
- No effect noted if studies relied on continuous data from standardized testing.
- Very few studies controlled for maternal depression.
- In several studies, nearly all the scores fell within normal range.

Malformations

- Serotonin thought to play a role in embryogenesis but different results for different SSRIs suggests other mechanisms may play a role as well.
- Important to remember that the incidence of many of the malformations in the general population is very low (~1 in 10,000).
- Increased incidence is still very low and mostly within general population numbers.
- Difficult to study.

Clinical Take Home Point

Antidepressants do not seem to worsen neurodevelopmental outcomes in offspring with the exception of a possible small risk of motor delay (SORT B).
Cardiac Malformations

Huybrechts et al 2014
- Population-based cohort of 64,389 Medicaid women
- NO increase in cardiac malformations with anti-depressant use in 1st trimester compared to untreated depressed women

Furu et al 2015
- Multicountry population-based cohort with sibling-discordant controls; huge sample (36,772 exposed)
- NO increase in cardiac malformations with SSRI or venlafaxine use in early pregnancy compared to sibling controls

Reefhuis et al 2015
- Bayesian analysis; confounding depression
- Fluoxetine - increased risk of RVOT obstruction
- Paroxetine - increased risk of RVOT obstruction and atrial septal defects

Winterfield et al 2015
- Multicenter cohort with SSRI-controls and non-exposed controls
- NO increase in major malformations with mirtazapine

Lassen et al 2016
- Systematic review of 14 studies
- NO increase in major malformations with venlafaxine or duloxetine (smaller data set)

Hendrick et al 2017
- Systematic review of studies
- Small variation in cardiac valve defects but small numbers and not controlled for confounders

Reefhuis et al 2015, 2015
- Quebec population-based cohort of >18K women
- Specific anti-depressant use in 1st trimester compared to untreated depressed/anxious women
- Fluoxetine - increased risk of several cardiac malformations and atrial/ventricular septal defects
- Sertraline - increased risk of atrial/ventricular septal defects in 2015 but not 2017 analysis

Gao et al 2017
- Systemic review and meta-analysis of 16 studies; confounding depression
- Slightly increased risk of cardiac valve malformations with fluoxetine in 1st trimester

Richardson et al 2019
- UK cohort of 3,897 pregnancies
- NO increase in major malformations with venlafaxine

Other Birth Defects/Malformations

Andrade 2014
- Review of 3 articles
- Difficult to draw consistent conclusions about duloxetine

Furu et al 2015
- NO increase in hypospadias, limb reductions, gastroschisis, cystic kidney, or craniosynostosis with SSRI or venlafaxine in early pregnancy
- Sertraline - 2-fold increase in omphalocele and 2.5-fold increase in anal atresia

Reefhuis et al 2015
- Fluoxetine - increased risk of cleft lip/palate
- Paroxetine - increased risk of anencephaly, gastroschisis, omphalocele

Winterfield et al 2015
- NO increase in major malformations with mirtazapine

Lassen et al 2016
- NO increase in major malformations with venlafaxine or duloxetine (smaller data set)

Berard et al 2017, 2015
- Increase with specific anti-depressant use in 1st trimester compared to untreated depressed/anxious women
- Citalopram - overall major malformations, musculoskeletal defects, congenital heart disease
- Non-sertraline SSRIs - increased risk craniosynostosis and musculoskeletal defects
- TCAs - eye, ear, face, neck and digestive defects
- Venlafaxine - respiratory defect

Gao et al 2017
- NO increase in specific malformations with fluoxetine in 1st trimester

Richardson et al 2019
- NO increase in major malformations with venlafaxine

Clinical Take Home Point

Since no antidepressant consistently has a risk of malformations above the general population, the best antidepressant to use in pregnancy (or preconception) is the last previously successful medication at the lowest effective dose (SORT B)

Poor Neonatal Adaptation

- Occurs in ~30% of infants exposed to anti-depressants in late pregnancy (but severity not agreed upon)
- Occurs usually within 4 days of life
- Not clear if withdrawal, toxicity, or other neurodevelopmental issue

Symptoms
- Jitteriness
- Difficulty consoling
- Feeding or sleeping problems
- Autonomic instability
- Tachypnea
- Hyponatremia/hypotension
- Seizures or seizure-like activity
Poor Neonatal Adaptation

- Poor neonatal adaptation does NOT appear to be dose-dependent
- Can occur with any anti-depressant
- SSRI > venlafaxine or mirtazapine (but underpowered); case reports of duloxetine
- Mixed data about impact of half-life
- Treatment is largely supportive
- Breastfeeding may be somewhat protective

Clinical Take Home Point

Parents should be warned about the risk of poor neonatal adaptation (SORT A) but you should not lower the effective dose or stop the antidepressant at the end of pregnancy to prevent it (SORT C)

Neonatal Seizures

- Overall incidence 1-3/1000
- SSRIs may increase neonatal seizures up to 5-fold
- TCAs may increase neonatal seizures up to 7-fold
- Unclear if dose-dependent
- Unclear if maternal psychiatric illness or other confounders (such as smoking or birth weight) play a role

Clinical Take Home Point

Parents should be warned about the risk of neonatal seizures (SORT A) but there is not enough data to guide treatment (SORT C)

Persistent Pulmonary Hypertension of the Newborn (PPHN)

- Potentially life-threatening event usually within hours of birth
- Deoxygenated blood enters systemic circulation due to high pulmonary vascular resistance
- Possible mechanism - serotonin is a potent pulmonary vasoconstrictor
- Prevalence 0.2% of live births but ~10% mortality

Clinical Take Home Point

- SSRI use in late pregnancy (after 20 weeks or 90 days before delivery) increased risk of PPHN
- NNTH ~300 (possibly higher)
- SSRI use in early pregnancy did NOT increase risk
- Non-SSRI use did NOT increase risk (but underpowered)

Based on Quebec cohort of 343,281 singleton pregnancies, US Medicaid cohort of 3,789,330 pregnancies, and systematic review and meta-analysis
### Clinical Take Home Point

Parents should be warned that SSRI use late in pregnancy increases the risk of PPHN (a potentially life-threatening condition) (SORT A)

### Pregnancy Outcomes

**Spontaneous Abortion**
- No increase with SSRIs or TCAs compared to untreated depressed women
- Increased risk with duloxetine compared to untreated depressed women
- Mixed data regarding venlafaxine and mirtazapine
- Bupropion with 3-fold higher risk compared to unexposed women but still remained within general population (control group unusually low)

Based on Danish population-based study of 1,005,319 pregnancies, UK cohort of 7,897 pregnancies, systematic review of 31 articles, cohort of 357 mirtazapine-exposed pregnancies, and systematic review of 8 articles


### Clinical Take Home Point

SSRIs and TCAs do not appear to increase the risk of spontaneous abortion (SORT A) but more study is needed for the other classes (SORT B)

### Pregnancy Outcomes

**Preterm Labor**
- Mixed results when antidepressant use compared to untreated depressed women
- One study showed mean difference of 2-3 days
- Slight increase when compared to siblings
- Up to 17% increase with SSRI use specifically

*No study looked at severity of depression*

Based on systematic review and meta-analysis of 8 studies, systematic review of 11 studies, Swedish retrospective cohort study of 1,580,629 pregnancies, systematic review of 16 studies


### Clinical Take Home Point

It is unclear whether antidepressants increase the risk of preterm birth, low birth weight, and small for gestational age but the impact does not appear to be clinically significant (SORT B)
Pregnancy Outcomes

Gestational Hypertension
- Consistencies in the literature: increased risk (1.2-2x) of gHTN with longer duration of use (continuing into second trimester and beyond), SNRIs associated with most risk.
- No increased risk with TCA alone
- 2016 study indicated increased risk of pre-eclampsia if using 2+ medications

Based on Dutch retrospective cohort study of 28,020 pregnancies, systematic review of 7 studies, American/Canadian retrospective cohort study of 3471 pregnancies


Pregnancy Outcomes

Postpartum Hemorrhage
- Increased risk (RR 1.53) of PPH in women exposed to any single antidepressant
- May be related to serotonergic function in platelet aggregation
- Risk of PPH with SNRI > SSRI; may be due to increased risk of HTN
- Matched cohort study: increased risk (aOR 1.5) of PPH in women using serotonergic medications, but even more increased risk (aOR 3.3) in women using other psych meds
- Mechanism of increased risk may not be entirely due to serotonergic effects, especially as antipsychotics are associated with increased platelet aggregation
- Increased risk with antidepressant use within 30 days of delivery compared to use earlier in pregnancy


Pregnancy Outcomes

Gestational Diabetes
- Single large Canadian nested case-control study: small increased risk (OR 1.19) of GDM with any anti-depressant use
- Venlafaxine: aOR 1.27
- Amitriptyline: aOR 1.53
- 2+ medication classes: aOR 1.38
- No increased risk with single SSRI
- Increased risk with longer exposure


Pregnancy Outcomes

Clinical Take Home Point

Antidepressants (especially SNRIs) in late pregnancy are associated with increased risk of gestational hypertension (SORT B) and postpartum hemorrhage (SORT B)
Venlafaxine and amitriptyline are associated with increased risk of gestational diabetes in a single study, but more research is needed (SORT C)

Peripartum Anxiety Disorders
- Prevalence: about 8-20% of pregnant women experience anxiety disorders
- Risk factors: history of anxiety disorder, mood disorder, high risk pregnancy
- Anxiety disorder during pregnancy is a risk factor for postpartum depression
- Risks associated with untreated anxiety disorders:
  - Low birth weight, preterm birth
  - Impaired maternal-infant bonding
  - Childhood behavioral and emotional problems
- ACOG: screen for anxiety disorders during pregnancy and in postpartum period


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Defining Anxiety Disorders

**Perinatal GAD** - Spectrum of anxiety symptoms (such as persistent and intense worry about a baby), inability to relax, physiological arousal
- Defining feature of an anxiety disorder is the interference with daily activities, worries that are recurrent, time-consuming, irrational, etc.

**Obsessive Compulsive Disorder** - Repeated, intrusive obsessive thoughts that are recognized as irrational and compulsive behaviors that are often related to protecting the baby (frequent checking, hand washing, etc.) that can occur prior to pregnancy and up to 1 year postpartum
- Up to 50% of women may have some symptoms without reaching level of disorder

**PTSD** - Precipitated by a traumatic experience (including a history of traumatic birth experience) and symptoms may include nightmares, hypervigilance, intrusive thoughts or re-experiencing of past trauma, irritable mood, the tendency to avoid disturbing stimuli, physiological arousal

**Panic Disorder** - Recurrent panic attacks (unpredictable moments of sudden intense fear accompanied by physical symptoms) with subsequent preoccupation with recurrence


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Generalized Anxiety Disorder

Perinatal anxiety disorders are common and there are risks if left untreated, so you should screen with a reliable screening tool during pregnancy and during the postpartum period, and treat appropriately (SORT C).
Neonatal Outcomes
Benzodiazepines and Treatment of Peripartum Anxiety Disorders
- CBT is first-line treatment, add medication in moderate/severe cases
- Mindfulness and relaxation techniques can be included
- Trauma-focused therapy for PTSD
- GAD: low-dose SSRIs (or SNRIs if has been the most effective in the past)
- Patients with anxiety may be more concerned about safety
- OCD: SSRIs, higher dose may be needed
- PTSD: SSRIs (ideally antidepressive) if no response to trauma-focused therapy
- BD: SSRIs can also consider low-dose lamotrigine if no comorbid depression or other anxiety disorder (though has been less well-studied)
- Benzodiazepines may be needed in the short-term for some patients with GAD or panic disorder


Clinical Take Home Point
- First-line treatment for anxiety disorders in pregnancy is CBT, but medications should be used if symptoms warrant (SORT C)

Benzodiazepines in Pregnancy
Benzodiazepines can be considered for use in GAD or panic disorder
- Goal is short-term use to help stabilize anxiety disorder
- Lorazepam is typically preferred agent due to shorter half-life
- Safest to use 3x/week or less
- Screen for substance use disorders and avoid in these patients

Benzodiazepines and Malformations
- In the past, concern for increased risk of cleft lip/palate - but this association was only found in case-control studies (subject to recall bias), and not in larger cohort studies
- Large UK population-based cohort study in 2014: no significant difference in rates of major congenital anomalies with use of benzodiazepines in first trimester of pregnancy
- No difference if benzodiazepines were used with or without SSRIs
- No difference compared to untreated psychiatric disorders
- 2013 review focused on outcomes for specific classes of benzodiazepines noted that one study showed increased risk of anorectal malformations with timizepam, but this was based on only 6 actual cases


Benzodiazepines and Neonatal Outcomes
- Premature birth: some increased risk, but also increased risk with untreated anxiety
- Respiratory Problems: overall mixed data on need for ventilatory support, but early study in n = 402 showed increased risk with late exposure vs early exposure
- Increased risk of NICU admissions seen with benzodiazepines
- Apgar Score: may be some increased risk for lower scores (>7 at 1 min, >5 at 5 min) with late benzodiazepine exposure, but overall mixed data in more recent studies
- "Floppy baby syndrome" (hypotonia, poor suck/feeding) associated with benzodiazepine use late in pregnancy reported in early case studies (1970s) but no increased risk seen in more recent studies
- Small association noted between prenatal benzodiazepine exposure and language competence at 3 years of age, even when benzodiazepines used in multiple trimesters of pregnancy
- No association between prenatal benzodiazepine exposure and language competence at 3 years of age, even when benzodiazepines used in multiple trimesters of pregnancy
- Clinical Take Home Point
- First-line treatment for anxiety disorders in pregnancy is CBT, but medications should be used if symptoms warrant (SORT C)
Clinical Take Home Point

Benzodiazepines can be used in pregnancy if indicated by maternal disease (SORT C)

Data on neonatal outcomes (respiratory support, hypotonia, low Apgar scores) and neurodevelopmental outcomes are mixed and studies have small sample sizes, so more research is needed to further explore these risks (SORT B)

Peripartum Insomnia

Insomnia

Prenatal
➢ Important to distinguish between physiologic changes and underlying psychiatric disorders

Postpartum
➢ Red flag for postpartum insomnia is inability to sleep while baby is sleeping
➢ Should avoid all sleep aids until infant schedule is identified and an alternate caregiver should be available

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Psychopharmacology for Insomnia

OTC Sleep Aids (Diphenhydramine)
➢ First line pharmacologic
➢ Several meta-analyses did NOT show increase in congenital malformations
➢ Limited data regarding obstetrical outcomes but appear reassuring

Melatonin
➢ Naturally made by placenta and important for fetal circadian rhythm and neuroprotection
➢ Not enough data but some theoretical concerns about supplementation so NOT recommended

Mirtazapine
➢ No studies found

Zolpidem
➢ One large study showed no increased risk of major malformations
➢ Increased adjusted OR for low birth weight, small for gestational age, preterm birth, and Cesarean delivery
➢ Comparison group included women with no psychiatric diagnosis

Trazodone
➢ Insufficient data but probably safe

First line treatment is CBT


Clinical Take Home Point

CBT or diphenhydramine are recommended for insomnia (SORT A), melatonin is not (SORT C), and the remainder lack data (SORT C)
Breastfeeding

- Most medications get into breast milk by passive diffusion (not active transport)
- Generally acceptable if neonatal level (RID = relative infant dose) is <10% of maternal level


SSRIs = Generally Safe
- Fluoxetine has highest estimated neonatal level due to long half-life
- Avoid if possible but should not switch if working for mom

Diphenhydramine = Generally Safe (RID 0.7-1.5%)

SNRIs = Probably Safe
- Venlafaxine has no adverse events reported but small numbers (RID 5.2-8.1%)
- Duloxetine has no adverse events reported but small numbers (RID 0.2-0.8%)

Benzodiazepines = Probably Safe
- 2 cases (1.6%) of CNS depression
- Caution with other CNS depressants (2nd benzo, anti-depressants, opioids)

Mirtazapine = Probably Safe (RID 0-2.9%)
- Small number of cases
- May increase neonatal somnolence and weight gain (per single case)

Zopiclone = Probably Safe
- No adverse event reported but small numbers (RID 1.45)

TCAs = Avoid
- Metabolites could accumulate
- Single case report of respiratory depression

Clinical Take Home Point

SSRIs and diphenhydramine are generally safe in breastfeeding with the possible exception of fluoxetine; TCAs should be avoided; the remainder are probably safe but understudied (SORT C)

Conclusions

Perinatal mental health remains underdiagnosed and undertreated

SSRIs are the most studied psychopharmacologic agents in pregnancy

Psychopharmacologic agents do have significant consequences in pregnancy and breastfeeding but should not be completely avoided, especially in the more severe cases

Questions?