ASSESSMENT AND MANAGEMENT OF MOOD AND ANXIETY DISORDERS IN THE PERINATAL PERIOD

CLAIRE DROM, MD

DISCLOSURES

NONE.

OBJECTIVES

- Understand how to **categorize psychiatric symptoms** in the perinatal period.
- Identify psychiatric treatment considerations **unique to the perinatal period**.
- Utilize **risk vs risk analysis** to choose first-line and second-line treatments for mood and anxiety disorders in the perinatal period.

A BIT OF EPIDEMIOLOGY

The reproductive years coincide with the typical age of onset of many psychiatric disorders

Most women with psychiatric disorders do have children

- Many of these pregnancies are UNPLANNED. Many can be UNWANTED
- Motherhood often becomes integral to a woman's existence

Prevalence

- Depression during pregnancy and post-partum: ~10%
- Anxiety disorders in pregnancy: 10-20%

Relapse rates during pregnancy:

- Depressive disorders:
  - Relapse rate in women ***taking medication*** for depression is 7-25% during pregnancy
  - Risk of relapse following discontinuation is 2x that of those who continue medication in pregnancy (in severe and recurrent depression) **50-60% !**
  - Risk of relapse in women with mild-moderate single episode depression after discontinuation is not elevated above baseline
- Anxiety disorders: not well characterized

Suicide is the #2 cause of death in the postpartum period

PERIPARTUM DEPRESSION

Associated with:

- Difficulties in breastfeeding, attachment, and domestic partnership
- Theorized deleterious consequences to the child's cognitive, psychological, and social developments through the lifespan

Risk factors

- Prior MDD, prior personal history of postpartum depression
- Possibly genetics (PPD in pregnant woman's bio mother)
- Psychosocial: STRESS (**parenting**, chronic, **perceived**), severe life events, IPV

Recurrence rates of PPD:

- ~1/3 of women who had PPD following first pregnancy will screen positive on EPDS after subsequent pregnancies
- Stress is likely a very significant mediator in subsequent episodes of PPD

PERIPARTUM DEPRESSION

"Baby Blues" vs MDD…. Baby blues are:

- Acute adjustment in the first ~2 weeks after childbirth. NOT pathological
- Experienced by the majority of women
- "Symptoms": irritability, changing moods, crying, "not feeling like myself"
- Lacking the distorted cognitions of MDD: shame, guilt, lack of desire to live, frank anhedonia, etc

Postpartum depression (PPD)

- Same symptoms of MDD. Distorted cognitions may center around themes of inadequacy as a mother with prominent guilt, shame, fear about ability to care for baby, etc.
- Onset of MDD criteria 4 weeks or later after childbirth
- New literature suggests that depression in the first 12 months after childbirth could be conceptualized as PPD
- Edinburgh Postnatal Depression Scale

ABNORMAL SYMPTOMS (separate from the ickiness of pregnancy and postpartum…)

- Lack of interest in pregnancy
- Guilt, sense of failure
- Suicidal ideation
- High anhedonia

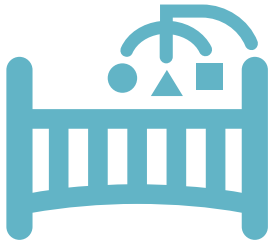
PERIPARTUM ANXIETY DISORDERS

- Includes: GAD, OCD, panic disorder, agoraphobia, specific phobias, PTSD, etc
- Less characterized than peripartum depression, but far more prevalent
- Pre- and post-natal prevalence rates vary
  - Prenatal 9-20%
  - Postpartum 11-20%
    - In a 2016 study of postpartum women, ~50% of a sample of 350 screened positive for anxiety disorder
- The peripartum period is associated with increase in first diagnosis/exacerbation of existing **OCD** (prevalence is ~2x in the peripartum compared to non-pregnant women)
- High sense of physiologic arousal (inability to relax), intrusive thoughts
- Screener: Perinatal Anxiety Screening Scale with cut off scores >26 (free PDF available online)

INTRUSIVE THOUGHTS

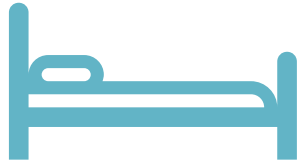
- What are they?
  - Unwanted thoughts that can pop into our heads without warning at any tim
  - In peripartum period, these thoughts usually center around the child's safety
  - Most often are ego-dystonic (meaning: the parent is quite upset by the content of thought and does not want it to happen)
  - Not specific for PPD or PAD but more common in PAD
  - **Can look like OCD, psychosis**
- How to ask:
  - 1. Attempt to normalize the experience: "*Many parents experience sudden, upsetting thoughts or images about something harming their baby. For most, they have no desire to think or act this way, and it's very upsetting to have such a thought. Has this happened to you at all?*"
  - 2. Assure limits of confidentiality – they will not be reported for child abuse/neglect unless they report actual actions towards such
- Parents may punish themselves physically and psychologically for having these thoughts
- Untreated, these thoughts contribute to psychological morbidity and interfere with parent-child attachment

ASSESSING SLEEP IN NEW MOMS



“Can you sleep when baby is sleeping?”

If not: “What prevents you from sleeping?”



“Do you have support for when you need to sleep?”

POST-PARTUM PSYCHOSIS

"*PUERPERAL PSYCHOSIS*"

- Delusions, hallucinations, marked confusion or appearing perplexed
- Will present within first 2-4 weeks after delivery
  - 50% of symptoms are present within the first 3 days after delivery
- Sudden onset, rapid deterioration, severe mood swings, and rapidly fluctuating symptoms
- Risk factors
  - Bipolar disorder
  - **Prior episode of post-partum psychosis (rate of recurrence approaches 100%)**
  - Half of women with PP Psychosis did not have suggestive risk factors
  - Family History
- Possible etiology
  - Sleep deprivation, dysregulation in immunoneuroendocrine system, genetic factors*
- ~50% will go on to meet diagnostic criteria for bipolar disorder or psychotic disorder

KEY POINTS

- Peripartum anxiety is more prevalent than depression
- Everyone can be a "hot mess" for the first two weeks after childbirth
- The "baby blues" are distinct from post-partum depression
- When assessing symptoms, they must be interpreted in the context of pregnancy and having a newborn. **Suicidal ideation, guilt, and frank anhedonia are indicators of a mood disorder**

TO TREAT OR NOT TO TREAT...

“ARE YOU CURRENTLY PREGNANT OR PLANNING TO BECOME PREGNANT IN THE NEXT YEAR?”

RISKS OF UNTREATED ANXIETY AND DEPRESSION

- UNTREATED maternal depression and anxiety:
  - Consistently associated with preterm birth and low birth weight

    **LBW is not changed in women with depression who are treated during pregnancy*
  - Thought to lead to higher risk of miscarriage and C-section
  - May contribute to factors such as increased smoking and substance use, hypertension, gestational DM, and pre-eclampsia
- Medications during pregnancy do not necessarily prevent postpartum onset of symptoms (*for mild-moderate depression*)
- Medications and therapy during pregnancy do not necessarily prevent these negative obstetric outcomes, either

ESSENTIAL TIME POINTS

Pre-conception	Intrapartum	Post-Partum	Lactation
• Laying the groundwork with psychoeducation • Maximizing physical and social health	• First trimester exposures • Managing changing physiology	• Discontinuation syndromes in the baby • Risk of post-partum psychosis	• Safety profiles of medications • Logistics of supporting breastfeeding

PRECONCEPTION COUNSELING

- Optimize physical and mental health
  - Encourage cessation of substance use and weight loss, if necessary
  - Protection from domestic violence
- Long-term conception options should be pursued if the woman does not want to become pregnant
- Provide psychoeducation as to how pregnancy may affect her illness
- Discuss risks of genetic transmission of illness to the child
- Ask yourself, "Would this medication be ***safe in the first trimester***?"

UNDERSTANDING THE DATA

- Source of Data: **WE HAVE NO RANDOMIZED CONTROLLED DATA IN THIS POPULATION**
  - Case reports: lowest quality of evidence
  - Pregnancy registries: can be helpful in gathering prospective data on outcomes to use for hypothesis formation
  - Retrospective population-based studies: often provide the largest sample size
- Difficult to establish a true control group when it comes to medication
  - *Example: Women with untreated GAD in pregnancy [control] vs women with GAD and taking medication[study]. Most data compares women without GAD and on no medications to women with GAD and on medication….apples and oranges*
- Explaining Relative Risk vs Absolute Risk
  - Patients need to be aware of their individualized risk, not the relative risk reported in the studies
- Similarly, they may need education on "statistically significant" vs "clinically relevant"

MEDICATION SELECTION
INTERPRETING THE RESEARCH

Maternal Risks

- Gestational diabetes and weight gain
- Hypertension and pre-eclampsia
- Movement disorders and toxicities
- Disease relapse
- Delivery procedures/outcomes

Fetal Risks

- Pre-term birth and miscarriage
- LBW, SGA, or LGA
- Malformations
- Cognitive and behavioral outcomes
- Discontinuation syndromes and medication side effects

"BACKGROUND RISK IS NEVER ZERO"

- Major malformations: 3-4%
- Premature delivery: 11-12%
- Gestational diabetes: 2-7%

RELATIVE RISK VS ABSOLUTE RISK: GUMGUM

A study of a new drug called GumGum found that some people who took the drug turned purple. Compared to people not taking GumGum, people taking the drug were **10 times more likely** to turn purple than those not on the drug. However, at baseline, in those not exposed to GumGum, the risk of turning purple is 0.01%.

So what is your individual risk of turning purple? If you don't take GumGum, you have a 0.01% risk (1 in 10,000) of turning purple. If you do take GumGum, your risk is 10 times that (0.1%), which translates to 1 in 1,000. Do you chance it?

NEW MEDICATION LABELING

- Pregnancy and Lactation Labeling Rule (PLLR) – by June 2020, all medications approved since 2001 should be moved from the A, B, C, D, X categories to PLLR
- Focus on HUMAN data with consideration of background risk
- Facilitate comprehensive risk vs risk discussions with patients by providing more information

Table 2. The Old Labeling Compared With the New

Section	Labeling Prior to the PLLR	New Labeling System
8.1	Pregnancy	Pregnancy (includes Labor and Delivery)
8.2	Labor and Delivery	Lactation
8.3	Nursing Mothers	Females and Males of Reproductive Potential (new section)
	Categories A, B, C, D, X	Categories removed

Abbreviation: PLLR = Pregnancy and Lactation Labeling Rule.

Table 3. New PLLR Format for Pregnancy Section 8.1 (Listed in Order)

Subsection	Description
Pregnancy Exposure Registry	Scientifically acceptable registry and contact information
Risk Summary	Known risks in context with background rates of adverse events in general and (if possible) in disease populations
Clinical Considerations	Medical/disease factors that should be considered
Data	Data that support the risk summary, with human data highlighted first

Abbreviation: PLLR = Pregnancy and Lactation Labeling Rule.

KEY POINTS: DECISION TO TREAT

- **Planning begins PRE-CONCEPTION** with all reproductive age women
- Untreated anxiety and depression have myriad effects on the pregnant mother and the developing fetus
- Treatment with medications (or psychotherapy) does not necessarily modify many gestational outcomes.
  - *Would argue that reducing suicide and improving mom's psychological health, wellbeing, and functional status are enormously beneficial for everyone involved…regardless of our ability to "measure" this*
- There exists a level of background risk of negative outcomes, irrespective of psychiatric diagnosis and treatment status
- Patients need to know **Relative Risk vs Absolute Risk** (individualized), as well as the difference between **statistical significance** and **clinical significance**

LET'S TALK MEDS

BIOLOGICAL FACTORS DURING PREGNANCY

In the mother

Decreased GI motility

Reduced protein drug binding

Increased hepatic metabolism

Increased volume of distribution

Increased GFR and renal clearance

In the fetus

More permeable blood-brain barrier

Reduced protein drug binding

Decreased hepatic function

BREASTFEEDING AND PHARMACOLOGY

Exposure in the infant depends on:

- Maternal plasma concentration
- Fraction of medication transferred in the breastmilk
- Infant's own absorption and elimination of the drug

Pharmacokinetic properties of the drug are important:

- Low molecular weight, low protein-binding, and lipophilic drugs transfer at higher rate
- Oral bioavailability
- Half-life

American Academy of Pediatrics says that a Relative Infant Dose (RID) of <10% is generally considered safe for ANY medication

ANTIDEPRESSANT SAFETY DATA IN PREGNANCY

- Meta-analyses have NOT SHOWN clinically relevant or statistically significant differences in: birth weight, birth length, gestation time, and APGAR scores in babies exposed to antidepressants as compared to non-exposed babies
- There may be a higher rate of miscarriage in these pregnancies, but whether this is due to maternal factors (like depression, high stress, smoking, etc) or antidepressant exposure is unknown
- May be a higher rate of NICU admissions in these babies.

ANTIDEPRESSANT SAFETY DATA IN PREGNANCY: CONGENITAL ANOMALIES

- Septal heart defects
  - Baseline risk in general population is 1%. ***At worst,*** the aggregate data suggests a risk in SSRI-exposed babies to be 1.5%
- Major Malformations (anencephaly, craniosynostosis, omphalocele)
  - Odds ratio of SSRI-exposed babies of 2.4-2.8

	Baseline risk	Individual risk if taking SSRI(SNRI)
Anencephaly	1 in 10,000 live births in US	1 in 5,000 (OR of 2.4)
Craniosynostosis	1 in 3,000	1 in 1,000 (OR of 2.5
Omphalocele	1 in 4,000	1 in 1,500 (OR 2.8)

ANTIDEPRESSANT SAFETY DATA IN PREGNANCY: PPHN

Persistent Pulmonary Hypertension of the Newborn

- Syndrome caused by a failure of the blood flow in the baby's lungs to transition after birth. It leads to high pressure in the circulatory system of the lungs and low oxygen in the blood.
- There was initially a warning on SSRIs causing PPHN. However, newer studies have failed to show a strong association between SSRIs and PPHN, and the FDA has removed its warning label for this condition.
  - Absolute risk is ~3 per 1,000 infants exposed to SSRI in 3rd trimester (baseline risk: 2 per 1,000 infants in the general population)

ANTIDEPRESSANT SAFETY DATA IN PREGNANCY: POOR NEONATAL ADAPTATION

- Most common adverse event clearly associated with exposure to SSRI during pregnancy
- Occurs in 30% of babies whose mothers have taken an SSRI in the 3rd trimester
- Symptoms:
  - Jitteriness, crying, poor feeding/sleeping, seizures (exceedingly rare)
  - Show up within minutes – hours after birth
  - Self-limited and resolve within 3-7 days with supportive care
- NOT DOSE-DEPENDENT → no reason to reduce the dose prior to delivery
- A "wash out" period prior to delivery does not prevent neonatal adaptation, either

ANTIDEPRESSANT SAFETY DATA IN PREGNANCY: NEURODEVELOPMENT

- Measured through assessment of: language skills, IQ, temperament, activity level, behavior problems
  - Usually in kids up to age 5-7yo (hard to follow-up for that long, however)
  - Cannot control for environment, parenting style, ACEs, etc
- Large 2017 population study was interesting (and alarmed the general public):
  - Without evaluation of confounding factors, antidepressant exposure associated with increased risk of intellectual disability. This association was absent after controlling for confounders
- Autism: 2015 meta-analysis showing association between SSRI exposure and autism. Association since repeated in other studies.
  - Risk of autism in general population: 1%. In the study: 1.5%
  - Not causative
  - Unclear if increased testing for ASD is leading to the increased rates to some degree (or if children exposed in utero are more likely to be tested for ASD)

SSRI AND SNRI SAFETY DATA IN PREGNANCY

- SSRIs are the best-studied (specifically, sertraline and fluoxetine)
  - Paroxetine: studies are back and forth about increased rates of cardiac defects in babies exposed in utero during the first trimester
  - "high dose" therapy not associated with change in effects to baby
- Of the SNRIs, venlafaxine has the most data, and safety information for all other medications in this class are considered with venlafaxine
  - Venlafaxine possibly associated with increased rate of miscarriage and hypertension, data is equivocal
- TCAs: remain highly effective, especially for anxiety disorders; quality of data in pregnancy is poor, possible increased risk of cardiac defects (unclear if greater than that from SSRIs, SNRIs)

SSRI AND SNRI SAFETY DATA IN LACTATION

- Sertraline, paroxetine, and fluvoxamine have the lowest transfer rate into breastmilk and are considered very safe
  - Sertraline has the most data and is considered the "safest"
- Fluoxetine and citalopram have higher transfer rate (still <10%) and are not considered first line in lactation

OTHER MEDICATION SAFETY IN PREGNANCY & LACTATION

- **Mirtazapine** – can be very helpful for insomnia and nausea (hyperemesis gravidarum!). May be too sedating in the postpartum period; weight gain may complicate the pregnancy
- **Bupropion** – has a pregnancy registry; studies show slight increase in miscarriage rates, low birthweight infants at high maternal doses (450mg QD); watch for increasing the risk of seizure/exacerbating pre-eclampsia
- **Buspirone** – no human data, probably okay
- **Hydroxyzine** – no good human data, but "probably okay" because Benadryl is safe; reduces breastmilk production
- **Beta Blockers** – no teratogenicity established; propranolol with highest association with fetal growth restriction; can cause hypoglycemia following delivery
- **Gabapentin** – limited human data; appears safe in the first trimester
- **Quetiapine** – weight gain may complicate pregnancy, although its use not associated with increased rates of GDM
- "newer" antidepressants: vortioxetine, vilazodone – no human data at this point, probably the same as SSRI/SNRI

BREASTFEEDING AND SLEEP

- Achieving consolidated sleep is VERY high priority for stabilizing psychiatric disorders
- May need to discourage exclusive nursing
- Can suggest:
  - Exclusive breastfeeding but pumping during the day to give bottles of breastmilk overnight
  - Formula supplementation at night
  - Partner or other supportive person to assist with nighttime feeds

SAFE SLEEP MEDICATIONS DURING PREGNANCY AND LACTATION

- **Assess for mom's comfort level with being sedated**
  - She may not want to be sedated!
  - ESPECIALLY postpartum
  - **Inquire about bed-sharing****
  - Short-acting medications may be preferable
- Recommended by ACOG: Unisom (doxylamine)
  - Trazodone is probably safe, but data is limited
  - **recommend avoidance of melatonin**
  - Benzodiazepines, zolpidem, and gabapentin commonly utilized on a PRN basis
- Anticholinergic medications (doxylamine, hydroxyzine, Benadryl) can reduce breast milk supply but have reassuring safety data in pregnancy

BENZODIAZEPINES

- Outcomes in Pregnancy:
  - Cleft lip/palate – data is equivocal. At this point, we don't think there's a clinically significant increase in malformations
  - Increased rate of miscarriage (spontaneous abortion, SA)
    - SA in 12-15% of all pregnancies
    - Large population-based studies have found rates of SA increased in BZD exposed pregnancies by **~50%** (again, hard to eliminate additional factors that lead to both the use of BZD and SA rate)
  - Associated with increased C-section delivery, low BW, neonatal respiratory intervention
- Implications at time of delivery:
  - "Floppy baby syndrome"
  - Withdrawal in the neonate
- Lactation considerations:
  - CNS depression in the breastfed infant is rare
  - Selecting a benzodiazepine with a shorter half-life is preferred
  - Lowest effective dose
- "as needed" use (<3 doses per week) is generally considered safe

DEPAKOTE (IS THE DEVIL)

- Strongly associated with numerous major malformations and thought to be the most teratogenic of all AEDs
  - Spina bifida (neural tube defects): increases risk by 12-16%
  - Atrial septal defect: increases risk by 2-3%
  - Cleft palate: increases risk by ~5%
  - Hypospadias: increases risk by ~5%
  - Polydactyly: increases risk by ~2%

Absolute Risk
Spina bifida 0.6%
ASD 0.5%
Cleft palate 0.3%
Hypospadias 0.7%
Polydactyly 0.2%

- **Average IQ loss of 10-points in children exposed in-utero**
- Folate supplementation
  - Questionable efficacy in prevention of neural tube defects in women taking valproate
- ANY REPRODUCTIVE AGE WOMAN ON DEPAKOTE SHOULD BE RECEIVING LONG-ACTING CONTRACEPTION

ZURANOLONE (MOVE OVER, BREXANOLONE)

- A subtype of postpartum depression may be due to fluctuations in allopregnanolone (neuroactive steroid) and GABA-A signaling after delivery
- Zuranolone is an allosteric modulator at the GABA-A receptor
- ROBIN (30mg daily) and SKYLARK trials (50mg daily) showed greater response with zur+antidepressant compared to placebo+antidepressant
  - Once daily dosing of 50mg for 14 days, in addition with stable dose of an antidepressant
  - Well-tolerated (somnolence, dizziness)
  - Symptoms MUST have begun in 3rd trimester or within first 4 weeks of delivery
- Not studied in lactation, bipolar illness, MDD with psychosis, anxiety disorders alone, or depressive symptoms with onset outside of this time period

ZURANOLONE

- Consider: no prior psych history and symptoms within first 6-8 weeks after delivery (or clearly starting late in 3rd trimester), severe symptoms requiring rapid improvement
  - No mood episodes earlier in pregnancy
  - Experts recommend this only for patients whose symptoms presented AFTER delivery
- For insurance to pay, must list "Postpartum depression" as the indication (not the correct DSM-5 name)
- While this was studied in severe MDD, could consider in mild-moderate PPD due to benign SE profile (insurers may not cover, however) and rapid response
- Very limited lactation data (n=14 but RID was <1%)
- Available in 20mg, 25mg, and 50mg capsules. Take in evening with fatty meal
- Box warning to avoid driving in first 12hr after taking doses

TAKEAWAYS FOR MEDICATION

Planning begins PRECONCEPTION. Before starting a medication, consider its safety in the first trimester and discuss with patient

If it's not broken, don't fix it

Use the lowest ***effective*** dose

Avoid exposures to multiple medications

May need dose increases later in pregnancy

Discuss plans for breastfeeding early and consider those when selecting a medication

THE RISK/BENEFIT CONVERSATION SUPPORTING AUTONOMY: A CHECKLIST

- Risks/benefits of NOT treating (both to mother and fetus)
- Educate on the changes in mental illness symptoms and presentation that may come with pregnancy and the post-partum period
- Risks to mother of stopping or continuing treatment
- Risks to fetus of treatment
  - Risks of major malformations (relevant in preconception and first trimester)
  - Should include any discontinuation syndromes after birth
  - Data on long-term outcomes
- Safety profile in breastfeeding
- Open discussion of Child Protective Services involvement
  - Take care to balance patient privacy and child safety
  - Limits of confidentiality

DOCUMENTATION TIPS

- No choice (to use medication or to discontinue medication) is without risk
- Document the period of stability on current regimen, diagnosis, current symptoms, and functional status. This is your explanation for wanting to continue therapy.
- Review the non-pharmacologic education and resources provided
- Discuss the risk of relapse if treatment is discontinued
- Discuss risks of medications chosen (if any)
- Document your efforts in collaboration

RESOURCES

- Mass General Hospital
  - www.womensmentalhealth.org
- MotherToBaby
  - Home Page - MotherToBaby
- Postpartum Support International
  - www.postpartum.net

QUESTIONS?

Claire.drom@centracare.com

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