EMOTIONAL COMPLICATIONS IN THE PERINATAL POPULATION

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Disclosures

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Objectives

- Identify ***concerning psychiatric symptoms*** in perinatal patients.
  - Depression and anxiety spectrum
  - Validated screening tools
  - Imminent risk/safety concerns
- Describe ***first-line treatment regimens*** for depression and anxiety spectrum disorders that are considered appropriate for use in treating both pregnant and lactating women.
  - FDA Pregnancy and Lactation Labeling Rule
  - First line treatment options
  - Risks to the fetus/infant of antidepressant use in pregnancy
  - Documentation

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Let's warm up…

Case Vignette #1

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- 27YO single woman, currently 25 weeks pregnant with her third child. Patient has a history of depression in the past, with recurrences, with one psychiatric hospitalization after a suicide attempt in her late teens. Multiple previous medication trials for depression. She had been relatively well-controlled on Vortioxetine (Trintellix) prior to pregnancy, but self-discontinued when she learned of her pregnancy. She now complains of depressed mood, poor sleep, and lethargy all the time, anxiety and sadness. Admits to having some difficulty in functioning, including caring for children and getting to work daily.
  - ☛ *What is your next step in the management of the patient's depression?*

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Identifying concerning psychiatric symptoms in perinatal patients.

- ☛Depression and anxiety spectrum symptoms
- ☛Validated screening tools
- ☛Imminent risk/safety concerns

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Depression

- DSM-5 criteria: **5 or more** symptoms present during the same **2-week period**, representing a **change from previous functioning**.
  - Either **depressed mood** or **anhedonia** must be present
  - Peripartum onset: onset during pregnancy or up to 1 year postpartum

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Depression

- Risk factors:
  - Personal history of affective illness
  - Marital discord
  - Inadequate social supports
  - Recent adverse life events
  - Lower socioeconomic status
  - Unwanted pregnancy

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Cohen L. & Nonacs R., 2005.

Depression

- Often overlooked in pregnancy…
  - Poor sleep
  - Appetite changes
  - Decreased energy
  - Decreased libido

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Cohen L. & Nonacs R., 2005.

Depression

- Symptoms to guide diagnosis…
  - ☛Lack of interest in pregnancy
  - ☛Profound anhedonia
  - ☛Guilty ruminations
  - ☛Suicidal ideation

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Cohen L. & Nonacs R., 2005.

Depression

- Be sure to screen for…
  - ☛Anemia
  - ☛Gestational Diabetes
  - ☛Thyroid dysfunction

All can present with depressive symptoms and may complicate the diagnosis of depression.

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Mood Symptoms in the Postpartum Period

Baby Blues	Postpartum Depression
• Affects 70-85% of women: ***Normal!***	• Affects ~10-15% of women
• Duration of symptoms <2 weeks	• Criteria for MDE
• Mild	• Tends to have later onset (2-4 weeks PP)
• Self-limited	• Severe/impairing symptoms usually present *(anhedonia, sense of failure, suicidality, psychosis)*
• Little to no intervention needed	

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Perinatal Anxiety

- Spectrum of anxiety symptoms occurring during pregnancy and/or the postpartum period
- Prevalence: as common as perinatal depression, 8.5-13% of women
- Symptoms:
  - ☛ Persistent and excessive worries
  - ☛ Inability to relax
  - ☛ Physiological arousal
  - ☛ **Intrusive thoughts = COMMON**

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Screening

The American College of Obstetricians and Gynecologists

COMMITTEE OPINION

- May 2015, American College of OB/GYN guidelines updated:
  - ☛ *"Clinicians screen patient at least once during the perinatal period for depression and anxiety symptoms using a standard, validated tool."*
  - ☛ *"Coupled with appropriate follow-up and treatment."*
  - ☛ *"Systems should be in place for ensuring follow-up for diagnosis and treatment."*

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Obstet Gynecol 2015.

Screening

U.S. Preventive Services TASK FORCE

- ☛ *"Recommends screening for depression in the general adult population, including pregnant and postpartum women. Screening should be implemented with adequate systems in place to ensure accurate diagnosis, effective treatment, and appropriate follow-up."*
- ☛ Other issues: Providers need to be cautious regarding misdiagnosis of bipolar disorder (e.g., need to screen for symptoms of mania), and screen for anxiety disorders.

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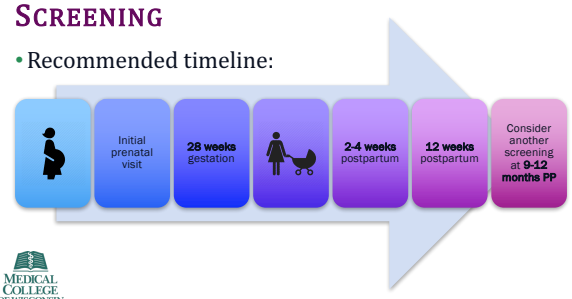
Siu AL, 2016.

Screening

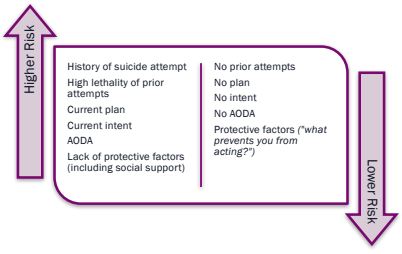
- Recommended timeline:



Screening: Principles

- Use a **validated screening tool** (most commonly used in pregnancy: EPDS and PHQ-9)
- Have **protocols** in place to address:
  - ☛ Score above cut-off OR acknowledgement of self-harm (or harm to baby)
  - ☛ Local mental health resources
  - ☛ Emergent resources (if imminent risk is a concern)
- **Normalize process**: acknowledge that you (or your practice) screen ALL women for mood and anxiety disorders during pregnancy and postpartum
- **Document** as part of an office visit

Suicidality (or Imminent Risk)



Thoughts of Harming Infant

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First line treatment.

- FDA Pregnancy and Lactation Labeling Rule
- First line treatment options
- Risks to the fetus/infant of antidepressants in pregnancy
- Documentation

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Pregnancy and Lactation Labeling Rule (PLLR)

- December 2014→ FDA published PLLR, with implementation over the following 3 years
- Narrative model of drug labeling
- Requires that pregnancy-related information be provided under 3 sections on the prescription label:
  - Pregnancy
  - Lactation
  - Females and males of reproductive potential
- Summarizes risks to the fetus, illness-related clinical considerations, and available safety data
- Replaces the "RISK" categories (A, B, C, D, X) categories, supports evidence-based decisions

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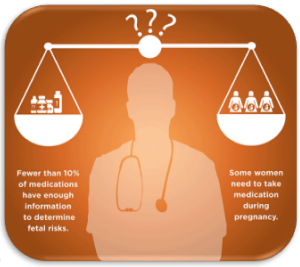
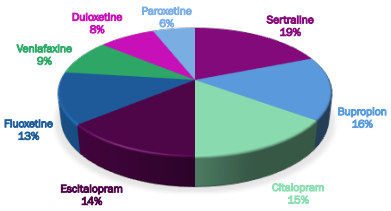
Striking A Balance…



TREATING for TWO
Safer Medication Use in Pregnancy

www.cdc.gov/treatingfortwo

Treating Depression



Dawson AL et al, 2016.

SSRIs (Selective Serotonin Reuptake Inhibitors)

- Represent 60-70% of new prescriptions for depression
- Easy to use, to dose
- High therapeutic index
- Generally well-tolerated, with following side effects:
  - ☛ Headaches
  - ☛ GI upset
  - ☛ Weight gain *(thought to be dependent on anticholinergic activity)*
  - ☛ **Sexual dysfunction**
  - ☛ Withdrawal syndrome

Fluoxetine (Prozac)
Sertraline (Zoloft)
Paroxetine (Paxil)
Citalopram (Celexa)
Escitalopram (Lexapro)
Fluvoxamine (Luvox)

SSRIs: What are the Risks?

- Congenital anomalies
- Poor pregnancy outcomes
- Poor neonatal adaptation
- Persistent pulmonary hypertension of the newborn (PPHN)
- Autism spectrum disorder

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SSRIs: Congenital Anomalies

- **No associations in prospective, controlled studies**
  - **None in meta-analyses of those studies**
- Retrospective case-control studies: some have not demonstrated increased risk
  - Some have suggested increased risk of:
    - Anencephaly (RR 2.4)
    - Craniosynostosis (RR 2.5)
    - Omphalocele (RR 2.8)
- Retrospective database reviews = controversial (increased risk of septal heart defects)
  - "Worst" data = 1.5% risk of cardiac defects *(general population = 1%)*

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Alwan S et al, 2007.
Huybrechts KF et al, 2014.

SSRIs: Pregnancy Outcomes

- A 2016 meta-analysis failed to find statistically significant and/or clinically relevant differences between antidepressant-exposed and non-exposed infants:
  - APGAR scores
  - Birth weight
  - Birth length
- Increased risk of ***preterm birth*** (OR 1.17, CI 1.1-1.25)
- Increased risk of ***spontaneous miscarriage***
- Increased risk of ***NICU admission***
- Poor neonatal adaptation…

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Eke AC et al, 2016.

SSRIs: Poor Neonatal Adaptation (PNA)

- Reports consistently indicate that ~25-30% of infants exposed to SSRIs in late pregnancy manifest symptoms of PNA
  - *Jitteriness, restlessness, irritability, increased muscle tone, rapid breathing*
- Symptoms are transient (average duration = 48 hours)
- Resolves spontaneously
- No specific medical intervention required
- Proposed etiologies: transient dysregulation of the infant's serotonergic system, increased reactivity of the HPA axis
- Recent studies have suggested that discontinuation of SSRIs late in the third trimester (to facilitate a "washout period") does NOT prevent this syndrome

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Kieviet N et al, 2016.
Kieviet N et al, 2016.
Kieviet N et al, 2015.
Warburton W et al, 2010.

SSRIs: Persistent Pulmonary Hypertension of the Newborn

- 2014 meta-analysis of 7 cohort and case-control studies:
  - Exposure to SSRIs in <u>early</u> pregnancy was not associated with PPHN
  - Exposure in <u>late</u> pregnancy (after 20 weeks) was associated with an increased risk of PPHN (OR = 2.50, CI 1.32-4.73, P = 0.005)
- *Things to consider:*
  - **Absolute risk** of PPHN is low (affects 1/1000 births in the general population; 0.3% represents estimated highest risk with maternal SSRI use)
  - Risk factors include **premature birth, maternal obesity, C-section, meconium aspiration, certain congenital malformations, smoking**
  - Studies included in the meta-analysis did not control for several confounding factors (including C-section, preterm birth, maternal obesity, or smoking– many of these factors are more common among women with depression)
- FDA– which once recommended a change in labeling for SSRIs to include a warning for PPHN– amended labeling in 2011 to reflect that a definitive link cannot be established

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Grigoriadis S et al, 2014.

SSRIs: Autism Spectrum Disorder

- Several epidemiologic studies demonstrated an association with prenatal exposure of SSRIs and ASD
- ***Beware confounding factors!***
  - Studies unable to distinguish between effects of drug exposure versus symptom exposure
  - Studies attempt to control for maternal mental illness, but no reliable measures of severity
- Data at face value: 87% risk
  - Average child = 1% risk *(SSRI exposure = 1.87%)*

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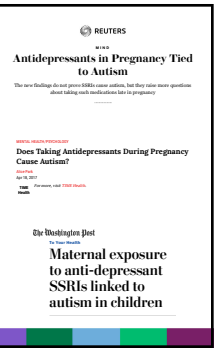
Boukhris T et al, 2015.


REUTERS

MIND

Antidepressants in Pregnancy Tied to Autism

The new findings do not prove SSRIs cause autism, but they raise more questions about taking such medications late in pregnancy

Does Taking Antidepressants During Pregnancy Cause Autism?

The Washington Post

To Your Health

Maternal exposure to anti-depressant SSRIs linked to autism in children

SNRIs in Pregnancy
(Serotonin-Norepinephrine Reuptake Inhibitors)

Venlafaxine (Effexor)
Desvenlafaxine (Pristiq)
Duloxetine (Cymbalta)

- *Risk of major congenital malformations after first-trimester exposure?*
- Possible increase in miscarriage
- Possible increased risk of **gestational hypertension**
  - ☛ Monitor BP closely with initiation and with dose increases
  - ☛ Concern if patient becomes pre-eclamptic
- No longer-term behavioral studies

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Lassen D et al, 2016.

Other Antidepressant Medications

- **Mirtazapine**
  - No known risk of major malformations
  - Side effect considerations:
    - Nausea less likely than with SSRIs; ***may be used with hyperemesis gravidarum***
    - ***Weight gain*** can increase obstetric complications
    - ***Sedation*** may be difficult to tolerate in pregnancy and postpartum, however can be helpful in patients struggling with insomnia
- **Bupropion**
  - ☛ No increased risk of congenital anomalies
  - ☛ Decreased birth weight at higher doses
  - ☛ Elevated rate of spontaneous miscarriage (p=0.009)
  - ☛ ***Lowers seizure threshold*** – possible risk in women with preeclampsia

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Smit M et al, 2015.
Guclu S et al, 2005.
Chun-Fai-Chan B et al, 2005.

What about Benzos?

- Early reports suggested in an increase risk of cleft lip/palate
  - ☛ ***Not confirmed by more recent studies!***
- Toxicity in newborns
  - ☛ Sedation, floppy baby syndrome, respiratory depression
- Concern for potential of physiological dependence and withdrawal for infant with chronic use throughout pregnancy

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Ban L et al, 2014.

The Risk of Untreated Psychiatric Symptoms

- ***Untreated psychiatric illness is not benign!***
  - Spontaneous abortion
  - Increased risk for congenital abnormalities (especially in cranial-neural crest derived structures (e.g., cleft lip/palate)
  - Preterm labor/preterm delivery
  - Low birth weight/fetal growth restriction
  - Preeclampsia
  - Behavioral concerns in children

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Glover V & O'Connor TG, 2002.

Documentation

- What should be documented:
  - Diagnosis, current symptom burden, period of stability, risk of relapse
  - Non-pharmacological management/treatment options
  - Specific risks of psychotropic exposure to developing fetus/breastfeeding infant dependent on gestational age
  - Specific risks of untreated psychiatric symptoms to developing fetus, dependent on gestational age
  - Educational resources provided to patient
  - How you collaborated with providers *(if applicable)*
- Review of drug monitoring database *(if available in your state)*
- Collaborate, discuss, pick up the phone to discuss/consult with other providers!

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Clinical Pearls/ Recommended Resources

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Preconception Planning

- 50% of pregnancies are unplanned.
  - ☛ *Rates are higher in women with psychiatric diagnoses!*
- Ask + document about birth control and/or conception planning.
  - ☛ **ONE KEY QUESTION**: ***"Would you like to become pregnant in the next year?"***
- Discussion of the risks at the time of prescription/ administration of medications, rather than awaiting conception.
- Encourage women to contact their mental health provider(s) immediately upon learning of pregnancy, prior to discontinuation of any medication.

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The National Campaign to Prevent Teen and Unplanned Pregnancy.

Psychopharmacology

During Pregnancy	During Lactation
• Return to a **previous effective medication**, if possible/appropriate. • **Monotherapy** is the goal *(but remission of symptoms trumps monotherapy)*. • Utilize lowest **effective** dose of medication. ☛ Majority of risks are **not** dose dependent. ☛ Avoid exposure of patient/fetus to both symptoms + medications. • Appropriate **monitoring** based upon drug regimen utilized.	• All psychotropic agents are secreted into breast milk, but concentrations may vary considerably. • AAP: "safe" breastfeeding ratio of infant dose exposure to maternal dose is <10%. ☛ **All antidepressant meds fall below the <10% cut off.** ☛ MOST psychotropic meds are compatible with breastfeeding. ☛ Exceptions: ▪ Lithium ▪ Lamotrigine • If taking antidepressants in pregnancy, continue the same medication during lactation to limit the infant's exposure to a single medication.

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Resources

- Websites:
  - ⌨ https://womensmentalhealth.org/
  - ⌨ https://nichd.nih.gov/ncmhep/initiatives/moms-mental-health-matters/
- Apps:
  - 📱 InfantRisk *(free!)*
  - 📱 Reprotox *(free for trainees!)*
  - 📱 MGHPDS *(free!)*

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Resources

THE PERISCOPE PROJECT
PERINATAL SPECIALTY CONSULT PSYCHIATRY EXTENSION

https://the-periscope-project.org/

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Case Vignette #1

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- 27YO single woman, currently 25 weeks pregnant with her third child. Patient has a history of depression in the past, with recurrences, with one psychiatric hospitalization after a suicide attempt in her late teens. Multiple previous medication trials for depression. She had been relatively well-controlled on Vortioxetine (Trintellix) prior to pregnancy, but self-discontinued when she learned of her pregnancy. She now complains of depressed mood, poor sleep, and lethargy all the time, anxiety and sadness. Admits to having some difficulty in functioning, including caring for children and getting to work daily.
  - ☛ *What is your next step in the management of the patient's depression?*

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Case Vignette #2

MEDICAL COLLEGE OF WISCONSIN

- 34YO married woman, no previous pregnancies, attorney, anticipating conception in the upcoming several months. Has struggled with insomnia for several years, currently managed on zolpidem 10 mg nightly. Questioning safety profile of utilization of zolpidem in pregnancy and would like to know her options prior to conception.
  - ☛ *What would be your next steps in the management of this patient?*

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Case Vignette #3

MEDICAL COLLEGE OF WISCONSIN

- 22YO single woman, in final year of college, currently 26 weeks pregnant. Pregnancy was unplanned. History of sexual assault as a teenager. Limited social support from FOB or family. Struggling primarily with anxiety symptoms surrounding life changes, worry about caring for infant independently, both financially and emotionally. Panic symptoms occurring several times weekly; she has started to miss classes/assignments in the past month. As pregnancy has progressed, there has been increased concern about delivery, likely stemming from trauma history. No previous psychotropic medication trials.
  - ☛ *What is your next step in the management of this patient?*

MEDICAL COLLEGE OF WISCONSIN

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QUESTIONS?

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