Perinatal Anxiety
Benzodiazepines
Risk-Risk Evaluation
Facilitator Guide

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Overview
This section focuses on a risk-risk analysis of medications in pregnancy (specifically, benzodiazepines) and includes non-medication options for addressing anxiety in the perinatal period.

Pre-session assignment
Before attending this session, please review the following references:

1) Yonkers KA, Gilstad-Hayden K, Forray A, Lipkind HS. Association of Panic Disorder, Generalized Anxiety Disorder, and Benzodiazepine Treatment During Pregnancy With Risk of Adverse Birth Outcomes. JAMA Psychiatry. 2017 Nov 1;74(11):1145-1152. doi: 10.1001/jamapsychiatry.2017.2733. PMID: 28903165; PMCID: PMC5710298.

2) Thorsness KR, Watson C, LaRusso EM. Perinatal anxiety: approach to diagnosis and management in the obstetric setting. Am J Obstet Gynecol. 2018 Oct;219(4):326-345. doi: 10.1016/j.ajog.2018.05.017. Epub 2018 May 24. PMID: 29803818.

3) Freeman MP, Góez-Mogollón L, McInerney KA, Davies AC, Church TR, Sosinsky AZ, Noe OB, Viguera AC, Cohen LS. Obstetrical and neonatal outcomes after benzodiazepine exposure during pregnancy: Results from a prospective registry of women with psychiatric disorders. Gen Hosp Psychiatry. 2018 Jul-Aug;53:73-79. doi: 10.1016/j.genhosppsych.2018.05.010. Epub 2018 May 29. PMID: 29958100.

Session
- **Discussion of case material (40 minutes)**
- **Wrap-up and Q+A (10 minutes)**

Learning Objectives
By the end of this module, the learner will be able to:
1. Discuss the risks of untreated anxiety in pregnancy and postpartum
2. Practice a risk-risk discussion regarding anxiety in pregnancy and postpartum
3. Appreciate the efficacy and safety of benzodiazepines in pregnancy and postpartum, including breastfeeding
4. Understand nonpharmacologic approaches to the management of anxiety in pregnancy and postpartum

Clinical Case Part 1

Andrea C is a 32-year-old patient referred to a reproductive psychiatrist for preconception counseling. She reports that she has a longstanding history of generalized anxiety disorder which has typically been well controlled on a combination of escitalopram at 10 mg PO daily and prn use of lorazepam 0.5 mg for moments of acute anxiety (uses no more than once every few weeks). She denies a history of PTSD, OCD, or panic symptoms.

She otherwise denies current or past depressed mood and all neurovegetative symptoms of depression. She denies suicidal ideation, intent, or plan, and she denies HI. She denies current or past symptoms of hypomania or mania including (but not limited to) grandiosity, distractibility, impulsive behaviors, racing thoughts, or decreased need for sleep. She denies all psychotic symptoms. She denies a history of substance use disorders and reports social alcohol use with no other drug use. Her past psychiatric history is notable for no suicide attempts or inpatient admissions.

She and her wife are planning to try to start to conceive in about the next six months and she recently visited a fertility center for her first work-up in preparation. She has had a prior discussion regarding the use of SSRIs in pregnancy [Click here to review risk-risk discussion] and has elected to stay on escitalopram throughout pregnancy and breastfeeding. However, she is not sure how to handle acute episodes of anxiety that tend to flare up related to her work or with caring for her father, who has dementia and resides in an assisted living facility. She wants to know what she can expect regarding her anxiety when she is pregnant.

FACILITATOR PAUSES FOR DISCUSSION

1) How common are anxiety symptoms in pregnancy?
Elicit the following:

- Relatively common in pregnancy, but often under-diagnosed and under-treated
- Roughly 10% of all women meet the criteria for generalized anxiety disorder (GAD) in pregnancy
- Highest rates of GAD tend to occur in the first trimester of pregnancy (may be hard to differentiate from pregnancy-related health concerns such as the risk of miscarriage)

2) What are the most important risk factors for anxiety in pregnancy?
Elicit the following:

- History of GAD is the strongest predictor of GAD in pregnancy
- Correlates with severity:
    - Women with four or more episodes of GAD are roughly seven times more likely to experience GAD in pregnancy

3) What is the impact of untreated anxiety in pregnancy?
Elicit the following:

- Increased risk of adverse birth outcomes, such as preterm labor, low birth weight, and pre-eclampsia
- Anxiety during pregnancy is also an independent risk factor for postpartum depression

Clinical Case Part 2

Her past medical history is unremarkable. She currently takes escitalopram 10 mg PO daily and Ativan 0.5 mg PO prn anxiety (typically 1-2 doses per month). Her family history is notable for a mother with severe anxiety well controlled on citalopram; no suicides, bipolar disorder, or postpartum issues. She works as an editor for an online journalism company. She has been married for two years. Her wife is a psychologist in private practice. They live in New York City.

ROS:
Psych: per HPI
MSK: within normal limits
All other systems reviewed and are negative

MSE:
Appearance: well groomed
Attitude: cooperative
Psychomotor: normal
Speech: normal rate, rhythm and tone
Mood: euthymic
Affect: calm
Thought Process: normal
Thought Content: issues with relationships
Cognition: intact
Language: fluent
Perceptions: no abnormalities
Consciousness: alert
Memory: intact
Intelligence: above average
Suicidal/homicidal ideation: denied
Impulse control: good
Insight/judgment: good
Reliability: reliable

During the session, Andrea and her psychiatrist discuss how she can manage her anxiety during pregnancy. She feels confident that her anxiety will "mostly be under control" with the escitalopram and wishes to stay on the current dose (higher doses in the past have been associated with vivid dreams and sexual dysfunction). She and her psychiatrist discuss monitoring her dose clinically throughout pregnancy [See Reproductive Life Cycle Progressive Case Conference]. She remains concerned about what to do acutely when the "anxiety is just over the top." She asks about the pros and cons of using lorazepam as needed during pregnancy. She also asks about what she can do from a non-medication standpoint to reduce her anxiety during pregnancy.

FACILITATOR PAUSES FOR DISCUSSION

1) What are the options for Andrea to further reduce her anxiety during pregnancy, given that she is already on escitalopram?
Elicit the following:

- With mild to moderate anxiety: cognitive-behavioral therapy and relaxation techniques have evidence of benefit and may reduce the need for medication
- There is also evidence to support stress reduction measures such as yoga, massage therapy, and acupuncture

- For moderate to severe anxiety/panic: consider increasing the dose of escitalopram before adding a benzodiazepine, in order to minimize polypharmacy in pregnancy and given metabolic changes in pregnancy
- For moderate to severe anxiety/panic, consider short-term use of a benzodiazepine.

2) What is the data regarding lorazepam use in pregnancy?
Elicit the following:

- Early reports suggested an association between lorazepam use in the first trimester and cleft lip/palate (estimated risk: 0.7%)
- More recent studies have not demonstrated this association
- Upon delivery, signs of toxicity have been reported, including sedation, decreased muscle tone, and respiratory compromise (may be related to higher maternal dose)
- There have also been case reports of neonatal withdrawal, including irritability, sleep disruption, and (rarely) seizure
- A systematic review and meta-analysis focusing on benzodiazepine use and delivery outcomes also noted an increased risk of several adverse outcomes, of which neonatal ICU (NICU) admission was the most clinically relevant
- Aim to use the minimum effective dose
- Aim to use medication with a shorter or intermediate half-life (such as lorazepam) as opposed to a longer half-life (such as diazepam), to reduce the level of exposure

3) What is the data regarding lorazepam use while breastfeeding?
Elicit the following:

- Lorazepam is excreted in low levels in breastmilk
- It is generally administered safely even directly to infants
- Evidence from nursing mothers suggests that lorazepam is not associated with any adverse effects with the usual maternal doses

References

1) Generalized anxiety disorder in pregnancy:

Buist A, Gorman N, Yonkers KA: Generalized anxiety disorder: course and risk factors in pregnancy. J Affect Disorder 2011: 131 (1-3), 277-283.

2) Benzodiazepines in pregnancy

Ban L, West J et al: First trimester exposure to anxiolytic and hypnotic drugs and the risks of major congenital anomalies: a United Kingdom population-based cohort study. PLoS One 2014: 9 (6); e100996.

Grigoriadis S, Graves L, Peer M, et al: Maternal anxiety during pregnancy and the association with adverse perinatal outcomes: systematic review and meta-analysis. J Clin Psychiatry 79(5):17r12011, 2018

Kelly LE, Poon S, Madadi P, et al: Neonatal benzodiazepine exposure during breastfeeding. J Pediatr 2012: 161 (3): 448-451.

3) Nonpharmacologic treatment of anxiety in pregnancy

Goodman J, Guarino A, Chenausky K, et al: CALM pregnancy: results of a pilot study of mindfulness-based cognitive therapy for perinatal anxiety. Arch Womens Ment Health 2014: 17 (5); 373-387.

Newham JJ, Wittkowski A, Hurley J, et al: Effects of antenatal yoga on maternal anxiety and depression: a randomized controlled trial. Depress Anxiety 2014: 31 (8): 631-40.

Nishimura A, Furugen A, Umazume T, Kitamura S, Soma M, Noshiro K, Takekuma Y, Sugawara M, Iseki K, Kobayashi M. Benzodiazepine Concentrations in the Breast Milk and Plasma of Nursing Mothers: Estimation of Relative Infant Dose. Breastfeed Med. 2021 May;16(5):424-431. doi: 10.1089/bfm.2020.0259. Epub 2021 Jan 15. PMID: 33449825.

Sockol LE: A systematic review for the efficacy of cognitive behavioral therapy for treating and preventing perinatal depression. J Affect Disord 2015: 177: 7-21.