Psychiatric Medication Management in Pregnancy and Breastfeeding

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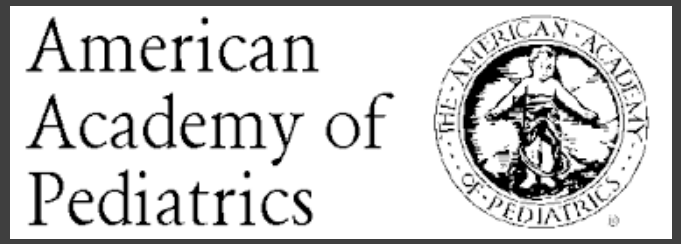
Disclosures

I have no disclosures to report

Learning Objectives

- Discuss the burden of perinatal mental illness
- Review principles of care
- Review SSRIs in pregnancy and breastfeeding
- Review insomnia management in pregnancy and breastfeeding

Perinatal mental health is recognized as a major public health problem



Maternal Mental Health and Suicide

- Mental health conditions are the MOST COMMON complication of pregnancy and childbirth, affecting 1 in 5 women and childbearing people (800,000 new parents each year in the United States).
- Suicide and overdose combined are the LEADING CAUSE of death for women in the first year following pregnancy.
- The peak incidence of suicide is 6-9 months postpartum.
- New mothers who die by suicide
  - Are mostly white and older
  - Use the most violent forms of suicide (hanging, jumping, shooting)
  - Die in the late postpartum period
  - Do not attend a postpartum obstetric visit (<50%)

General Principles

- Revisit diagnosis and verify it yourself
- Classify severity of illness
- Maximize use of Behavioral and Somatic Treatments and Interventions
  - Bright light therapy is an underutilized tool and has evidence of benefit alone or in combo
- Minimize the number of adverse exposures
  - Don’t expose to both illness and meds – treat to remission
- Use Medications with Data when possible
- Assess other risks (Smoking, Marijuana Use) when making a plan
- **Educate Everyone**

General Treatment Principles:
Expect Pregnancy

- By age 44, 85% of US women will be mothers.
- Unexpected pregnancy makeup 50% of all pregnancies in the United States.
- It is essential to discuss pregnancy safety when a medication is prescribed.

Case

Daniella Lopez is a 33-yr old married female being seen in her PCP's office. She is on Prozac 20 mg, Clonazepam 0.5 mg PO PRN for management of Generalized Anxiety Disorder and Major Depressive Disorder. She was started on medication 9 months after the birth of her first child. She has been on them for over a year and has residual symptoms of insomnia and anxiety.

She wants to have another baby but doesn't want to feel as bad as she did before. She is conflicted about what to do and asks you for guidance. Specifically, She wants to know about the risk to her baby if she gets depressed again.

What do you tell her?

Depression During Pregnancy – Impact on baby – Physical

Depression during pregnancy has been associated with:

- Preterm delivery
- Low birthweight
- Higher rates of preeclampsia and gestational diabetes,
- Decreased infant motor tone and activity
- Higher infant cortisol levels and poor reflexes, and overall worse infant health status

(Ashman et al. 2002; Diego et al. 2004; Essex et al. 2002; Field et al. 2010; Halligan et al. 2004; Lee et al. 2009; Orr et al 2007)

Depression During Pregnancy – Impact on baby - Neuropsychiatric

Mother's postpartum depression has been shown to have the following effects on infants and developing children

- Lower IQ
- Slower language development
- High rates of ADHD
- Behavioral problems
- Psychiatric illness

Grace at all 2003

Case continued..

You have reviewed the risk of maternal depression to the baby.

Her psychiatric hx is notable for one suicide attempt in her 20s. Her most recent depressive episode was quite severe and was the 3rd depressive episode of her life. She has responded to Prozac well. She is currently in partial remission with continued symptoms of insomnia, anxiety and low energy.

She is worried about the impact of medication use in pregnancy. She asks you what the risk are – what do you tell her?

Psychotropic Drug in Pregnancy

- Risk – Risk discussion
- Collaborative, patient-centered approach required
- No one drug is “the one”
- No one study covers everything
- Use medications when the risk of disorder outweighs the risk of treatment
- Patients with similar presentations can make very different decisions regarding treatment

SSRIs in Pregnancy

Congenital

- No increased risk in congenital abnormalities

Neonatal

- Neonatal Adaptation Syndrome.

Gestational

- Antidepressant-exposed babies weigh, on average, 97 grams (3.4 ounces) less than unexposed babies.

Neurobehavioral

- Antidepressant dose and duration during pregnancy did not predict any cognitive or behavioral outcome in children 3 to 6 years exposed to SSRIs, tricyclics, or venlafaxine *(Nulman et al., 2012, 2015)*

Cardiac Defects and PPHN

- In 2005 FDA issued a warning concerning heart defects with Paroxetine.
- Large studies and metanalyses have found no association between SSRI use in first trimester and overall congenital or heart defects.
- Persistent Pulmonary HTN
  - In 2006 the FDA issued an alert b/w SSRI usage and Persistent Pulmonary Hypertension of Newborn (Chambers et al. 2006)
  - Subsequent studies were done with only 50% confirming the finding
  - Huybrechts et al. 2015- looked at 4,000,000 women and the association disappeared when they controlled for confounders

SSRIs and Autism Spectrum Disorders

- This assumption was raised by earlier studies that had major confounds. These early epidemiologic studies showed an association between SSRI use during pregnancy and ASD in the children. Croen et al 2011, Rai et al 2013
- Since then, there have been more careful studies (sibling controls and propensity matching) that have dismissed this finding.

Case continued..

Daniella presents to her OB office for her first visit. She is 10 weeks pregnant with her second child. She has continued to take Prozac 20mg and occasionally uses the Clonazepam.

Her medical hx is notable for Type 2 diabetes, BMI of 32.

She is doing well overall however, she is unable to sleep at night. She is managing by taking naps when she gets home from work however, that's not ideal for her toddler and family. She is reporting worsening fatigue.

What risk does insomnia pose for her?

Risks conferred by Perinatal Insomnia

Increased rates of Gestational Diabetes (Facco et al. 2017)

Higher rates of prolonged labor and delivery (Lee and Gay 2004)

Preterm Birth (Felder et al. 2017; Okun et al. 2011)

Near miss MVA for new parents (Malish et al. 2016)

Also associated with perinatal depression and anxiety, mood changes immediately after birth and postpartum psychosis.

Case continued..

Given Daniella's risk you review sleep hygiene, refer to CBT-I and suggested the VA CBTI coach app. She returns with persistent insomnia and is becoming more and more fatigued and irritable. She now describes feeling demoralized. She states, "if I could sleep, I think I could handle things better".

Given her case so far – what do you review?

What medications would you consider for sleep management in pregnancy?

Benzodiazepines

- Commonly prescribed during pregnancy
- Account for 1—4% of prescriptions with highest use in the 3rd trimester
- Lorazepam is the most commonly prescribed benzo in Pregnancy
- They cross the placenta and are present in the amniotic fluid.
- They also cross the fetal blood-brain barrier.

Reproductive Safety of Benzodiazepines

Lengthy debate on congenital malformations, gestational outcomes and neonatal outcomes

Congenital Outcomes

- Newer data is reassuring with reference to benzo use in isolation.
- However, a recent systematic review (Grigoriadis et al. 2019) noted that concurrent use of benzodiazepine and an anti depressant in pregnancy was associated with an increased risk of malformations.

Reproductive Safety of Benzodiazepines

Gestational Outcomes

- Several studies have noted an association b/w benzodiazepine use and adverse outcomes early in pregnancy such as miscarriage
- Recent cohort study (1.6 million women) noted an association b/w benzo exposure prior to conception and an increased risk of ectopic pregnancy. (Wall- Wieler et al 2020.)

Reproductive Safety of Benzodiazepines

Breastfeeding

- Reassuring data if a bit sparse
- Kelley et al 2012 analyzed 124 infants exposed to benzos through breastmilk
- Adverse effects including infant sedation, were rare, observed in 2 infants and both moms were taking more than 1 med at the time
- General recommendation is to avoid longer acting benzos given their extended presence in breastmilk

Conclusion

Discuss reproductive safety when prescribing

Not considered first line

Hypnotic benzodiazepine receptor agonists

- We don’t know much
- They cross the placenta
- Zolpidem – several small studies found no increased risk of congenital malformations
- Zolpidem and adverse obstetrical outcomes - several small studies have found an association between use and preterm birth low birth weight, SGA and C section. – Confounding factors such as depression, anxiety or smoking status were not controlled for.
- Zolpidem has different recommended dosages for women versus men.

Z Drugs - Risk of Major Malformations – Two Studies

Wikner (2011) Swedish birth medical registry

- 1341 exposed to Z-drug (Zopiclone 692, Zolpidem 603, Zalepion 32)
- 42 infants (3.1%) in the Z-drug group had a malformation
- Did not look at individual medications

Wang (2010) Taiwan

- 2497 exposed to Zolpidem
- No increase in risk of malformations
- Worse outcomes – LBW, preterm birth, SGA, caesarean birth
- Limited number of exposures to zopiclone and zaleplon
- No data on frequency of use: as needed vs. daily
- High rates of polypharmacy
- Mothers using Z-drugs tended to be older, more likely smokers

Conclusion?

- Some, but not all, studies have shown worse pregnancy outcomes among women using Z-drugs during pregnancy, including increased risk for low birth weight, small for gestational age, preterm birth, caesarean section, and NICU admission. *
- The recent studies are reassuring and do not show any increase in risk of major malformations in infants exposed to Z-drugs during pregnancy.
- We can’t fully rely on them due to the limitations. As such we can’t confidently determine the risk of malformations.

Sedating Antihistamines

Widespread use of diphenhydramine, hydroxyzine, and doxylamine

Used for anxiety sleep, pruritis, nausea and vomiting

Despite use we have limited data

They don’t appear to be related to congenital malformations

Trazodone

- Not studied as a sole agent in pregnancy
- Trazodone has been demonstrated to improve sleep continuity.
- The data we do have shows that Trazodone can reduce postpartum depressive symptoms when given for insomnia in the third trimester.
- No increased risk of birth defects in prospective controlled studies that included trazodone along with other antidepressants.
- No adverse reactions have been reported to date in breastfeeding babies.

Mirtazapine

- 2016 review 31 papers, 390 exposed neonates
- No increased risk of birth defects. 334 mirtazapine-exposed cases, the incidence of major malformations did not differ from the incidence observed in children exposed to other antidepressants or non-teratogenic medications
- Lactation: Four papers noted 11 cases of exposure to Mirtazapine through lactation and noted no adverse effects
- 6 papers reported on Neurobehavioral outcomes (N=22) (ages 1.5 month- 12 months) No adverse effects on behavioral development were noted.
- Increased rate of preterm birth (confounds not ruled out).
- Hyperemesis Gravidarum – Case reports suggesting efficacy in doses of 30mg
- Sedation and weight gain are common side effects.
- Available as disintegrating tablet

Smit M, Dolman KM, Honig A. Mirtazapine in pregnancy and lactation – A systematic review. Eur Neuropsychopharmacol. 2016 Jan;26(1):126-35

Alternative Treatments

- Buspar – Human Data limited, animal data shows no congenital malformations
- SSRIs and SNRIs for treatment of anxiety, depression
- Seroquel – lowest placental passage of the SGA's 23.8%, Lowest transference to milk out of SGAs- class risks apply

Melatonin & Pregnancy

- Melatonin (1 to 3 mg) elevates blood melatonin levels up to 20 times normal levels.
- During pregnancy, night-time concentrations of melatonin increase steadily after 24 weeks of gestation.
- Melatonin has roles in fetal maturation and the onset of labor
- Most of the melatonin research comes from animal studies
- In animal studies, it has been shown that supplementation with melatonin decreases the risk of pre-eclampsia, preterm birth and intrauterine growth retardation (IUGR).

Case continued..

Daniella is now 36 weeks pregnant, and her spouse accompanies her to her appointment. He expresses concern for her postpartum mental health. She had deteriorated after her last delivery and delays in identification, establishment of care and the time for the medication to work made things worse. He is more aware of local resources and feels reassured that she is currently on Prozac.

He asks you if she decompensates if there is anything quick, safe and effective?

Brexanolone

- FDA approval in 2019
- Rapid onset of benefit, durable efficacy to 30 days
- IV delivered analogue of allopregnanolone
- Allosteric modulator of GABA receptors
- Two positive, controlled trials in postpartum depression (onset during late pregnancy or postpartum, presented within six months postpartum with MDD)
- Implementation challenges: cost, in hospital

Post Partum Support International (PSI)

- Great resource for both providers and patients
- Provider options
  - Perinatal Psychiatric Consult Line
  - Provider Directory
  - PSI conference
  - Perinatal Mental Health Certification (PMH_C)

Provider Education/ Support Resources

- Education
  - MGH Center for Women's Mental Health
  - National Curriculum for Reproductive Psychiatry
  - Marce Society – MONA (Marce of North America)
  - NASPOG (North American Society for Psychological Obstetrics and Gynecology)
  - BUMPS(Best use of Medicines in Pregnancy) Leaflets produce by UK Teratology Information Services
  - Perinatal Mental Health Toolkit by the RCGP (Royal College of General Practitioners)
  - NAMS North American Menopause Society
- Consult
- Bio ethics committees
- Risk management

Resources

- MothertoBaby: (866) 626-6847 / www.mothertobaby.org
- Motherisk.org: (877) 439-2744 / www.motherisk.org
- Infantrisk.com: (806) 352-2519 / www.infantrisk.com
- Reprotox: www.reprotox.org
- LactMed: www.lactmed.nlm.nih.gov
- E-Lactania: www.e-lactancia.org/ingles/inicio.asp
- Toxicology Data Network: www.toxnet.nlm.nih.gov

Local Resources

Tucson Postpartum Warmline 888-434-MOMS (6667)

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- Available in English and Spanish
- Phone volunteers are ready to assist you by simply listening or by helping you find a resource in your area.
- If you leave a message a volunteer will return your call between 9AM and 8PM.

Breastfeeding support

- La Leche League Tucson – www.lllofaz.org/Tucson.html
  - 520-789-MILK
- Milk and Honey @ milkandhoneytucson.com
- Mama's Latte – 520-628-4202
- TMC Women's Breastfeeding Support Group 520-324-5730
- Northwest Women's Center Breastfeeding Support Group – currently virtual. 520-877-4156

Tucson Postpartum Depression Coalition

Tucson Postpartum Depression Coalition (TPDC) is a non-profit, charitable organization committed to improving the lives of mothers by promoting the emotional health of pregnant and postpartum mothers in Pima County- There is a resource list that is routinely updated.

In Home Family Support

Nurse-Family Partnership is a community healthcare program that will connect families with a nurse home visitor.

*(*For prenatal first-time mothers) starting from pregnancy to second birthday

Serving Maricopa and Pima

In Home Family Support

Child & Family RESOURCES INC.
Where Great Things Start Small

- **Healthy Families Arizona:** Healthy Families Arizona is a free program that helps mothers and fathers become the best parents they can be. (***For infants 3 months and under)***
- Teach and support appropriate parent child interaction and discipline
- Provide periodic developmental assessments and referrals if delayed
- Link families with community services, health care, childcare, and housing Available in Mohave, Pima, Cochise, Pinal, Graham, SantaCruz, Maricopa, Yuma and Yavapai county

In Home Family Support

- FREE home visitation program that works with pregnant women, mothers of young children and their families.
- Pregnant women and families with children enrolled in the program receive additional supports such as navigating access to prenatal care; family medical care; and assistance in applying for AHCCCS, WIC and other program that help you and your family thrive..
- They have translation services that allow them to work with a variety of women, including many refugees. ***(Pregnant Women or mothers with children up to 24 months old.)***

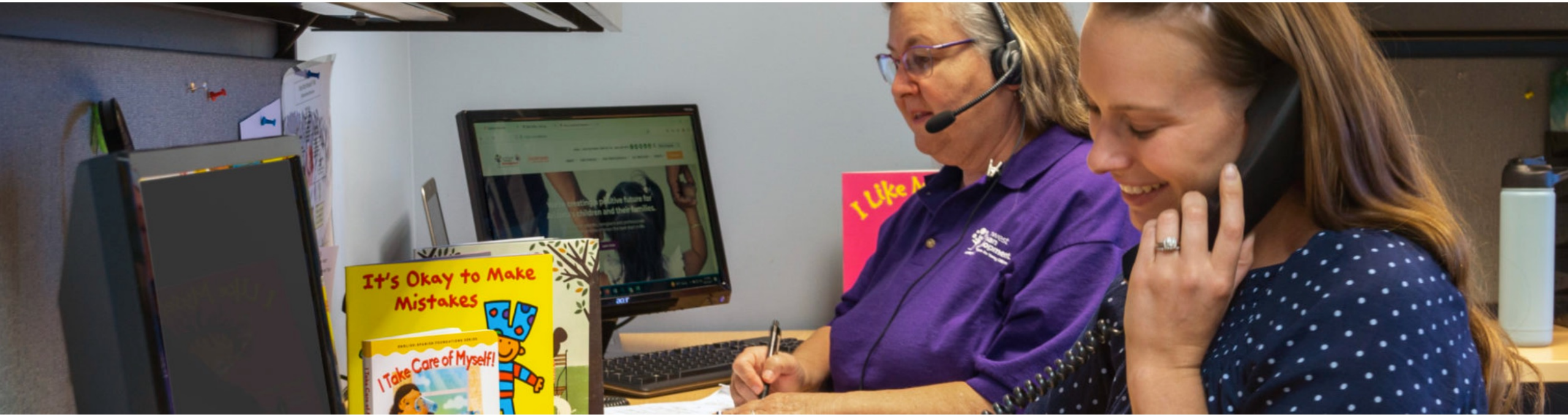
Pima County Parent Coalition

This is a great web page. It works as a triage for both information and referrals for both in-home and community based parent education programs

The referral is on the page, they have an easy to use link and form.
The resources offered are:

- In Home Class
- Community Class
- Educational Development for Children
- Learning how to Improve Parenting Skills
- Getting Children Ready for School
- Learning how to Keep Children Healthy
- Learning how to Better Manage Stress
- Behavior Management
- Healthy Pregnancy and Childbirth

PIMA COUNTY PC PC PARENTING COALITION



BIRTH TO FIVE HELPLINE™

Call 877-705-KIDS (5437) for Free Child Development Support

Birth to Five HELPLINE

Starting out right

- *SOR provides* health education and supportive services to pregnant and parenting adolescents ages 21 and younger, regardless of their financial situation.
- Several classes including pregnancy health education classes, parenting education classes, healthy relationship classes.
- Supportive services such as case management, support groups, free pregnancy classes, a scholarship program
- Jensen's Corner– a boutique of gently used baby and maternity items to purchase with *SOR* incentive dollars.

SOR
Starting Out Right

a program of Arizona Youth Partnership

2-1-1 Arizona

Provides contact information for a wide range of services including:

- Food and meal services
- Housing and Shelter
- Income and Expenses
- Rent and Utility Expenses
- Employment services
- Pets and animals

The site is accessible by county

Others

Southern Arizona Diaper Bank

Care Resource and Referral is a FREE statewide program in Arizona that helps families find childcare to fit their needs.

Addiction/Recovery

The Haven

IOP

Residential

Outpatient

Las Amigas – Residential recovery program