Project TEACH
FAMILIES THRIVE WITH GOOD MENTAL HEALTH

Pharmacotherapy approaches for perinatal depression and anxiety

NEW YORK STATE | Office of Mental Health

Speaker:

Kristina M. Deligiannidis, M.D.

- Director, Women's Behavioral Health, Zucker Hillside Hospital, Northwell Health
- Medical Director, Reproductive Psychiatry, Project TEACH
- Professor of Psychiatry, Molecular Medicine and Obstetrics & Gynecology, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell
- Professor, Feinstein Institutes for Medical Research

Contact: kdeligian1@northwell.edu

Disclosures

I disclose the following financial relationships: contracted research and consultant for Sage Therapeutics; consultant for Gerbera Therapeutics, Lipocine, Reunion Neuroscience and GH Research; grant funding from the NIH.

The silent storm

Diagnosing unipolar perinatal depression

Major depressive disorder with peripartum onset

includes 5 of the following symptoms, one of which must be either depressed mood or decreased interest or pleasure, beginning in pregnancy or within 4 weeks of delivery and causing impairment of functioning

- Depressed mood, often overshadowed by severe anxiety, crying episodes
- Markedly diminished interest or pleasure in activities- do not enjoy family, baby
- Appetite disturbance- food has no taste, forces self to eat, poor gestational wt
- Sleep disturbance- cannot fall or stay asleep
- Physical agitation (on-edge) or feeling slowed down
- Fatigue, exhausted
- Feelings of worthlessness or excessive or inappropriate guilt
- Decreased concentration or ability to make decisions
- Recurrent thoughts of death or suicidal ideation –my family would be better off without me

†Symptoms must be present most of the day nearly every day for two weeks.

ProjectTEACH
FAMILIES THRIVE WITH GOOD MENTAL HEALTH

Distinguishing Baby Blues From PPD

	Baby Blues	Postpartum Depression
Prevalence	40-75% of mothers	14% of mothers
Onset	First few days after delivery, typically peaking on fourth or fifth day	Typically emerges in pregnancy and approx. 2 months postpartum
Duration	A few hours or a few days, remitting spontaneously within 2 weeks of delivery	Longer than 2 weeks; can last up to 3 years
Severity	Mild symptoms (mood lability, tearfulness, anxiety, irritability)	Clinical diagnosis of major depressive episode
Impaired functioning	No	Yes
Symptom resolution	**Resolves spontaneously**	Requires treatment
Association with psychopathology	Unrelated to psychiatric history and not predictive of future problems	More common in women with history of major depression and bipolar disorder and predictive of future depressive episodes

ProjectTEACH
FAMILIES THRIVE WITH GOOD MENTAL HEALTH

Perinatal anxiety disorders

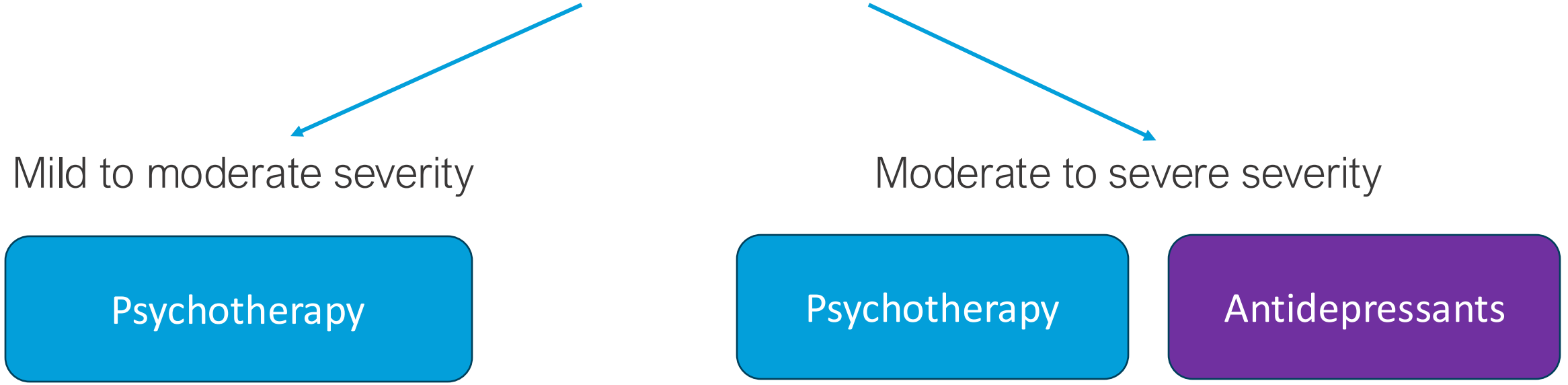
- group of distinct but interrelated conditions characterized by excessive fear, elevated emotional response to perceived/real threat, and related behavioral disturbances
- overall prevalence of having at least 1 or more anxiety disorder is estimated to be 20.7% (1 in 5) (Fawcett EJ et al 2019)
- high co-morbidity of anxious symptoms with perinatal depression, up to 50%
- generalized anxiety disorder: excessive worry that is difficult to control, agitation, irritability, easy fatigue, sleep disturbance
- obsessive compulsive disorder: time-consuming and functionally impairing intrusive, unwanted, thoughts/images/urges (obsessions) and repetitive behaviors or mental acts performed to relieve the anxiety from obsessions (compulsions)

Untreated perinatal depressive/anxiety disorders are associated with adverse maternal, obstetrical and child developmental outcomes

- Decreased maternal functioning (Field, T, 2010)
- Psychosis, suicidal ideation, homicidal ideation and suicide attempt are psychiatric emergencies that lead to psychiatric hospitalization, maternal death (Rodriguez-Cabezas et al, 2019)
- Bidirectional relationship between depression and gestational diabetes mellitus (Fischer et al, 2023)
- Preterm labor (Bansil P et al, 2010) ,preterm birth (Grigoriadis S et al, 2013), stillbirth/neonatal death and hypertensive disorders of pregnancy (Staub et al, 2012, Thombre et al, 2015, Delanerolle et al, 2022)
- Increased requirement for surgical delivery interventions (Wang SY & Chen CH, 2010) and cesarean delivery (Bansil P et al, 2010)
- Inadequate maternal-infant bonding prenatally and post-delivery (Rossen et al, 2016; Betcher et al, 2020, Dagher et al, 2021)
- Lactation failure or unplanned weaning (Dennis CL & McQueen K, 2009; Stuebe AM et al, 2014)
- Impaired child cognitive development (Tuovinen S et al, 2018), behavioral and emotional development (Leis JA et al, 2014; Pearson RM et al, 2013)
- Impaired child brain development/antenatal stress from mental illness is associated with accelerated development of offspring neural networks via fetal (developmental) programming (Schinost D et al, 2016; Rotem-Kohavi, N et al, 2020)

ProjectTEACH
FAMILIES THRIVE WITH GOOD MENTAL HEALTH

Treatment of perinatal depressive and anxiety disorders



ProjectTEACH
FAMILIES THRIVE WITH GOOD MENTAL HEALTH

Poll

When your patient with recurring episodes of depression and chronic anxiety (well treated with fluoxetine 40mg and clonazepam 1mg) becomes pregnant, do you:

a) Panic!

b) Advise that both medications should be discontinued and not restarted until 2nd trimester.

c) Advise that both medications should be discontinued during pregnancy and not restarted until she is done breastfeeding.

d) Advise to stop fluoxetine and clonazepam and switch to sertraline.

e) Continue both medications at current doses and call Project TEACH for phone consultation.

ProjectTEACH
FAMILIES THRIVE WITH GOOD MENTAL HEALTH

Antidepressants for perinatal depression and anxiety

Serotonergic antidepressants (SSRI, SNRI, etc.): **moderate/severe** unipolar perinatal depression

- *No* randomized, placebo-controlled trials (RCT) of antidepressants for antenatal depression
- Meta-analysis of 11 postpartum RCTs showed that there may be a benefit of SSRIs over placebo in response (55% versus 43%; pooled risk ratio (RR) 1.27, 95% CI 0.97 to 1.66) and remission (42% versus 27%; RR 1.54, 95% CI 0.99 to 2.41) at 5 to 12 weeks' follow-up. (Brown JVE et al, Cochrane Database Syst Rev, 2021)
- Antepartum vs postpartum use is associated with different risks
- Treatment approach: titrate until efficacy/tolerability then treat acute episode at that dose -> once reach euthymia, continue treatment (continuation phase) for several months (or longer) to prevent relapse.
- Often best to combine with psychotherapies

ProjectTEACH
FAMILIES THRIVE WITH GOOD MENTAL HEALTH

Antidepressant dosing for perinatal depression and anxiety (see drug labels at: https://dailymed.nlm.nih.gov for full prescribing info)

Medication	Indication	Starting dose	Usual dosage range
Fluoxetine	MDD, GAD, OCD	10 mg	10 – 80 mg daily
Sertraline	MDD, GAD, OCD	25 mg	50 – 200 mg daily
Escitalopram	MDD, GAD	5 mg	5-20 mg daily
Citalopram	MDD, GAD	10 mg	10-40 mg daily
Paroxetine	MDD, GAD, OCD	10 mg	10 – 50 mg daily
Venlafaxine	MDD, GAD	37.5 mg	75-225 mg daily
Bupropion XL	MDD w/o anxious distress Nicotine dependence	150 mg	150 – 450 mg daily
Mirtazapine	MDD with nausea	7.5 mg	15 -45 mg nightly

Which antidepressant for which pregnant patient?

SSRIs and SNRIs are the main groups of medications used in the treatment of perinatal depression and anxiety

If the patient has never been on the medication, a medication with a short half-life and low concentration in the breastmilk such as sertraline should be recommended

If the patient has a history of previous medication trials, it is recommended to use medications that were helpful in the past and resulted in remission of symptoms

How to start and monitor treatment with SSRI/SNRI?

Start low and discuss with the patient the most common side effects such as gastrointestinal distress, headache, and possible activation such as temporary increase in anxiety

Discuss with a patient that it usually takes 4-6 weeks for the patient to notice benefits

At each visit, check for possible side effects and use screening tools (e.g., PHQ, EPDS) at each visit to help you monitor the response

Increase the dose based on clinical presentation, the goal of the treatment is complete remission of symptoms

As metabolism of many antidepressants increases later in pregnancy, patients in the third trimester might need a dose increase to compensate for the lower active dose circulating in the blood

1st trimester: 1 to 13
2nd trimester: 14 to 27
3rd trimesters: 28 to 40

Prenatal antidepressant use and fetal malformation risk

Birth defects affect one in every 33 infants (about 3%) born in the US annually (healthy, no meds) Data and Statistics on Birth Defects | Birth Defects | CDC

Overall, no increased risk or a small absolute increased risk of congenital malformations with 1st trimester use of SSRI/SNRIs

small absolute risk increase of cardiac malformations with OR of 1.28 (CI:1.17-1.41) for any antidepressant, OR of 1.69 for SNRI and 1.25 for SSRI (De Vries C, 2021)

large cohort study of 949,504 pregnant women suggested no substantial increase in the risk of cardiac malformations attributable to antidepressant use during the first trimester (Huybrecht et al., 2014)

small increased RR of overall major congenital malformations (RR=1.1, CI: 1.03-1.19) with SSRI use, however no significantly increased risk was observed when restricted to women with a psychiatric diagnosis (RR 1.04, 95% CI 0.95 to 1.13) (Gao SY et al 2018)

ACOG recommends all women of reproductive age take a prenatal vitamin with at least 400mcg of folic acid, starting at least one month before pregnancy and continuing through the first 12 weeks.

ProjectTEACH
FAMILIES THRIVE WITH GOOD MENTAL HEALTH

Prenatal antidepressant use and birth outcomes

- US preterm birth rate =10.41% https://www.cdc.gov/nchs/data/vsrr/vsrr038.pdf
- increased risk of moderate-to-late preterm birth (Rommel at al., 2022):
  - gestational age: 2.3 day decrease in gestational age
  - birthweight: 51 g decrease in birthweight
  - other outcomes: higher risk of moderately low birthweight, postnatal adaptation syndrome, and neonatal admission
  - no differences were found for persistent pulmonary hypertension or birth defects

Prenatal antidepressant use and neonatal complications

Postnatal adaptation syndrome (PNAS):

infant irritability, abnormal crying, tremor, lethargy, hypoactivity, decreased feeding, tachypnea, respiratory distress, irritability, hypothermia, and hypoglycemia

- severity and length are impacted by multiple factors including dose, timing and duration of exposure and SSRI pharmacology including half-life, presence of active metabolites and maternal and infant metabolism, etc.
- delayed neonatal adaptation occurred in 11.2% of exposed vs 4.4% of unexposed infants RR 2.52 (CI 2.36 to 2.70) (Cornet et al, 2024)
- most often been reported after exposure to escitalopram and venlafaxine
- symptoms can last through 1st month postnatal life; discontinuing 3rd trimester antidepressant use does not reduce PNAS risk (Salisbury AL 2016)

ProjectTEACH
FAMILIES THRIVE WITH GOOD MENTAL HEALTH

Prenatal antidepressant use and neonatal complications

Persistent pulmonary hypertension of the newborn (PPHN): can result whenever cardiopulmonary transition does not occur

- Reduced length of gestation and premature birth has been associated with increased risk of PPHN
- 1.9/1000 gen pop vs. 2.9-3.5/1000 w late gestation SSRI use (Becker M et al, 2016; Huybrecht et al., 2015) but no association found by Rommel AS et al, 2022
- NNH=285 for 1 infant to develop PPHN with late gestation SSRI exposure (Norby U, 2016)
- Infants with PPHN present within twelve hours of birth with cyanosis and mild respiratory distress and can develop severe respiratory failure requiring intubation and mechanical ventilation
- PPHN can be fatal in approximately 10-20% of cases

ProjectTEACH
FAMILIES THRIVE WITH GOOD MENTAL HEALTH

Prenatal antidepressant use and child development

Antidepressant exposure compared with no exposure was not associated with an increased risk of autism spectrum disorder or ADHD (Brown et al., 2017; Malm H et al, 2016; Rommel AS et al, 2020; Vega ML et al, 2020)

Women with depression during pregnancy have an increased risk of having a child with autism spectrum disorder, regardless of antidepressant use (Wilcox Hagberg et al, 2018).

ProjectTEACH
FAMILIES THRIVE WITH GOOD MENTAL HEALTH

FDA approved rapid-acting antidepressant for postpartum depression

Zuranolone is a synthetic analog of the natural neuroactive steroid allopregnanolone which is a metabolite of progesterone.

Zuranolone is believed to work through GABA receptors (not serotonin)

- first oral FDA-approved treatment for moderate-severe PPD approved in 2023
- once daily oral dosing (50mg PO qPM x 14 days only)
- rapid-acting antidepressant effects at day 15, as early as day 3, maintained through day 45 (Deligiannidis K et al 2021, and 2023)
- **boxed warning** for impaired ability to drive or engage in other hazardous activities due to CNS depressant effects
- may be used alone or as an adjunct to oral antidepressant therapy, but avoid other CNS depressants
- schedule IV
- take with fat-containing food around 8pm

Dosing for postpartum depression

(see https://dailymed.nlm.nih.gov for full prescribing info)

Medication Generic	Medication Trade	Recommended dosage
Zuranolone	Zurzuvae	50mg PO qPM x 14 days, if excessive sedation reduce dose to 40mg PO qPM; total course not to exceed 14 days treatment

There is no up or down-titration for the medication
It is a single acute treatment course (14 days only)
Postpartum use only (not in pregnancy) with onset of PPD during pregnancy or after delivery up to 1 year
Specialty pharmacy
Not for use in bipolar disorder (has not been well studied and is not FDA approved for that use)

Antidepressant side effects

Sertraline (SSRI)

- Nausea (26%)
- Diarrhea/loose stools (18%)
- Insomnia (16%)
- Somnolence (13%)
- Dry mouth (16%)
- Tremor (11%)

Zuranolone (neurosteroid)

- Somnolence (36%)
- Dizziness (13%)
- Diarrhea (6%)
- Fatigue (5%)
- Urinary track infection (5%)

all data from
https://dailymed.nlm.nih.gov/dailymed/index.cfm

ProjectTEACH
FAMILIES THRIVE WITH GOOD MENTAL HEALTH

Use of antidepressants during lactation

World Health Organization and The American Academy of Pediatrics recommends that children are breastfed for their first 2 years of life.

The American Academy of Family Physicians and the American Dietetic Association recommend exclusive breastfeeding for the first 6 months of life and breastfeeding with complementary food from 6 months until at least 12 months of age and as long thereafter as desired.

Antidepressant use should not discourage women from breastfeeding; overwhelming benefits of breastfeeding usually outweigh risks of medication use in women with unipolar depression +/- anxiety

- PND is associated with ↓ breastfeeding duration and ↑ breastfeeding difficulties (Dennis CL 2009)
- Relative infant doses (RID) less than 10% of maternal dosage are generally acceptable per FDA
- Side effects to watch for: sedation, irritability, poor feeding, GI upset

- The National Library of Medicine at the NIH maintains the Drugs and Lactation Database (LactMed) found at: https://www.ncbi.nlm.nih.gov/books/NBK501922/
  - This useful database is maintained by a peer review panel who reviews scientific data to assure validity and currency. It includes information on levels of drugs in breastmilk and infant blood and the possible adverse effects in the nursing infant.

Infant exposure to antidepressants via breastmilk

Use NIH database (LACT MED) to look up meds: https://www.ncbi.nlm.nih.gov/books/NBK501922/

Antidepressant Relative Infant Doses in %

- Bupropion 0.2-2.0
- Citalopram 3-10
- Desvenlafaxine 5.5-8.1
- Doxepin: AVOID: reports of hypotonia, sedation, vomiting, suppressed respiratory rate, weight loss
- Duloxetine <1
- Escitalopram 5.2-7.9
- Fluoxetine 0.6-14.6 (long half-life)
- Fluvoxamine <2
- Mirtazepine 0.5-3
- Nortriptyline 0.87-3.71 (watch for dry mouth, constipation, urinary retention)- favored tricyclic in lactation
- Paroxetine 1.2-2.8
- Sertraline 0.4-3
- Venlafaxine 6-9
- Zuranolone <1

ProjectTEACH
FAMILIES THRIVE WITH GOOD MENTAL HEALTH

Perinatal benzodiazepine use

Benzodiazepines are indicated for short-term use only. Longer term use should be avoided.

- increased risk of congenital malformations with combo antenatal benzo/SSRI use (OR=1.40 (CI:1.09-1.80) (Oberlander TF et al, 2008; Grigoriadis S et al 2019)
  - Prenatal benzo use *not* associated with increased risk congenital malformations (OR: 1.13; CI:0.99-1.3) including first trimester specifically (OR=1.08; CI:0.93-1.25) (Grigoriadis S et al 2019)
  - Prenatal benzo use *not* associated with cardiac malformations (OR: 1.27; CI:0.98-1.65) (Grigoriadis S et al 2019)
- single study noted potential increased OR for Dandy-walker malformation (any benzo), anophthalmia or microphthalmia and esophageal stenosis (alprazolam) and pulmonary valve stenosis (lorazepam) (Tinker SC et al 2019).
- **neonatal withdrawal syndrome: floppy baby syndrome**: poor tone, lethargy, hypothermia, low APGAR (Yonkers KA et al 2017); also hypertonia, hyperreflexia and tremors (Iqbal MM et al, 2002); worse neurobehavioral outcomes in SSRI + benzo than SSRI alone or depressed alone (Salisbury AL, 2016)
- increased rates of ventilator support, cesarean section and low birth weight (Yonkers KA et al 2017)
- symptoms of floppy baby syndrome can appear shortly after delivery to 3 weeks after delivery and last for several months

Perinatal benzodiazepine use

- **Benzodiazepines with shorter half-lives and no/few active metabolites preferred over mid to long-acting (e.g., lorazepam, not clonazepam, not diazepam).**

- In term neonates (>37 weeks GA), elimination is extended due to poor hepatic function (immature Phase II metabolism). Neonates born prematurely can have prolonged plasma elimination (and thus increased side effects).

- Alprazolam: 13hr half-life; RID=3%- I do not prescribe due to increased risk of dependency

- Lorazepam: 14hr half-life (85% bound to plasma proteins; RID=2.5%, low levels in breastmilk-medication of choice

- Clonazepam: 20-50hr half-life; RID=2.8, LactMed recommends use of shorter half-life benzo over clonazepam

- Diazepam: 30-60hr half-life for parent drug plus 30-100 hours major active metabolite dimethyldiazepam; RID = 7.1% , LactMed recommends use of shorter half-life benzo

ProjectTEACH
FAMILIES THRIVE WITH GOOD MENTAL HEALTH

Clinical considerations

- First and foremost, consider how you would treat the patient's unipolar depression/anxiety if the patient was not pregnant/lactating.

- Consider…
  - the risk to the patient and the fetus/infant of stopping or reducing current pharmacotherapies
    - Risk of untreated illness to patient and fetus/infant
  - the risk to the patient and the fetus/infant of continuing those pharmacotherapies
    - Consider antenatal vs. postnatal (lactational) risks
  - the risk of switching to an alternative pharmacotherapy
    - Is the alternative really safer? Will the alternative control depressive/anxiety symptoms as well as the current regimen?

Clinical considerations

- When possible, any changes to a medication regimen should be made prior to conception to ensure symptom stability and to minimize exposure to the fetus. Abrupt discontinuation of antidepressants in pregnant women with a history of depression is associated with high risk of relapse without known benefit (L.S. Cohen et al., 2006).
  - Preconception planning!

- Women with history of recurrent unipolar MDD or history of symptom recurrence associated with past reduction or discontinuation of antidepressants **should not discontinue their antidepressant during pregnancy.**

- If SSRI/SNRI dose increased in pregnancy, monitor for side effects after delivery, can decide when to reduce SSRI/SNRI dose (if at all) once reassured of continued euthymia; don't immediately resume pre-pregnancy dose as could precipitate MDD relapse.

Clinical considerations

Frequently the best option is a medication that the patient found helpful in the past, due to known efficacy and tolerability

When possible, monotherapy in adequate dose is preferred over polypharmacy

The goal of treatment is full symptom remission, and medications should be adjusted to the lowest efficacious and fully therapeutic dose

Project TEACH is here to help.

Call us: 1-855-227-7272

M-F 9a-5p

ProjectTEACH
FAMILIES THRIVE WITH GOOD MENTAL HEALTH