Perinatal Psychopharmacology

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Faculty Disclosure

- **Dr. Freeman**: Consultant/Advisory Board—Alkermes, Otsuka, Sunovion; Investigator Initiated Trials (Research)—JayMac; Grant/Research—All research funding through Massachusetts General Hospital (MGH): investigator initiated research/sponsored: JayMac, Sage; Dr. Freeman works with the MGH National Pregnancy Registry [Current Registry Sponsors: Teva (2018–present), Alkermes, Inc. (2016–Present), Otsuka America Pharmaceutical, Inc. (2008–Present), Forest/Actavis (2016–Present), Sunovion Pharmaceuticals, Inc. (2011–Present)]. As an employee of MGH, Dr. Freeman works with the MGH Clinical Trials Network and Institute, which has had research funding from multiple pharmaceutical companies.

Disclosure

- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).
  - Dr. Freeman will be discussing off-label use and/or investigational use of prescription medications/medical devices in the presentation and will identify those issues.

- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.

- This activity has been independently reviewed for balance.

Learning Objectives

- Balance the risks and benefits of different treatment options for perinatal depression
- Describe the risks and benefits of different treatment options for bipolar disorder across pregnancy and the postpartum
- Assess pharmacologic treatment options in women of reproductive age from onset of treatment initiation

When Do Disorders Start?

- “Mental illnesses are the chronic diseases of the young”
- One-half of all diagnoses presented by age 14
- Three-quarters by age 24

Kessler RC, et al. *Arch Gen Psychiatry*. 2005;62(6):593-602. Insel TR, et al. *Arch Gen Psychiatry*. 2005;62(6):590-592.

Treating Women of Childbearing Potential

- 49% of pregnancies in the United States are unintended
- 80% of teen pregnancies are unintended
- 82% of US women have had a child by age 40

Centers for Disease Control and Prevention. Unintended Pregnancy Prevention. www.cdc.gov/reproductivehealth/UnintendedPregnancy/index.htm. Accessed June 3, 2019. Martinez G, et al. Centers for Disease Control and Prevention. National Health Statistics Reports. Number 51. April 12, 2012.

CDC Recommendations for Women of Reproductive Age

- Take folic acid
- Maintain healthy diet and weight
- Regular physical activity
- Quit/abstain from tobacco use, alcohol, and drugs
- Communicate with health care providers about screening and management of chronic diseases
- Use effective contraception correctly if one is sexually active and wishing to delay/avoid pregnancy

Centers for Disease Control and Prevention. Unintended Pregnancy Prevention. www.cdc.gov/reproductivehealth/UnintendedPregnancy/index.htm. Accessed June 3, 2019.

Context for Assessing Risk

- Rate of major malformations: 3% to 4%
- Rate of premature delivery: 11% to 12%
- Rate of gestational diabetes: 2% to 7%
- Untreated psychiatric disorders carry risks for woman and baby
- Alcohol and tobacco use prevalent in patients with untreated psychiatric disorders
- Obesity increases obstetrical risks

March of Dimes. www.marchofdimes.org/pregnancy.aspx. Accessed June 3, 2019. Centers for Disease Control and Prevention. www.cdc.gov/reproductivehealth/index.htm. Accessed June 3, 2019. Nonacs R, et al. *J Clin Psychiatry*. 2002;63 Suppl 7:24-30. King JC, et al. *Clin Obstet Gynecol*. 1983;26(2):437-448.

Risks of Untreated Antenatal Depression

Possible Complications

- May negatively affect maternal weight gain
- May increase the risk of low birth weight, prematurity, and small for gestational age
- Neonatal behavioral differences, such as irritability and decreased activity
- May lead to less adherence with prenatal care

Wisner KL, et al. *JAMA*. 1999;282(13):1264-1269. Wisner KL, et al. *Am J Psychiatry*. 2009;166(5):557-566. Mulder EJ, et al. *Early Hum Dev*. 2002;70(1-2):3-14. Yonkers KA, et al. *Obstet Gynecol*. 2009;114(3):703-713.

Risks of Untreated Anxiety during Pregnancy

Potential Physiological Risks

- Fetal exposure to increased cortisol; higher anxiety symptom burden associated with higher maternal plasma and amniotic fluid cortisol levels, catecholamines
- May result in maternal vasoconstriction and limit oxygen and nutrient delivery to fetus
- Impact on long-term CNS development
  - Longitudinal cohort study, investigators demonstrated that children exposed *in utero* to perinatal anxiety are at increased risk for attentional problems at age 5 and 14

CNS = central nervous system.

Ross LE, et al. *J Clin Psychiatry*. 2006;67(8):1285-1298. Rambelli C, et al. *J Affect Disord*. 2009;122(1-2):139-143. Meshberg-Cohen S, et al. *Compr Psychiatry*. 2007;48(6):504-510. Chen YH, et al. *J Affect Disord*. 2010;120(1-3):258-262. Lou HC, et al. *Dev Med Child Neurol*. 1994;36(9):826-832. Lou HC, et al. *Lancet*. 1992;340(8810):54. Acs N, et al. *Birth Defects Res A Clin Mol Teratol*. 2006;76(4):253-261. Glover V, et al. *Psychoneuroendocrinology*. 2009;34(3):430-435. Clavarino AM, et al. *J Atten Disord*. 2010;13(6):658-667.

Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format

Guidance for Industry

DRAFT GUIDANCE

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologic Evaluation and Research (CBER)

December 2014
Labeling

The Pregnancy and Lactation Labeling Rule (PLLR) or "Final Rule"

- Subsections
  - Pregnancy
  - Lactation
  - Females and Males of Reproductive Potential
- **Pregnancy Exposure Registry**
  - Scientifically acceptable registry and contact info
- **Risk Summary**
  - Human, animal, pharmacologic data
  - Adverse developmental outcomes
  - Background risks from the US population (ie, CDC data)
- Context
  - Includes information about background rates of adverse events
  - Risks to be quantitatively compared to the risk for the same outcome in infants born to women not exposed to the drug, but who have the disease or condition for which the drug is indicated (ie, appropriate controls)

US Food and Drug Administration. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf. Accessed June 3, 2019.

APA/ACOG Joint Recommendations

- **Psychotherapy: First-line for mild-to-moderate MDD**
- Lifestyle components: Nutrition, weight management, prenatal care, childbirth education; treatment for substance abuse
- **Women trying to conceive who have histories of MDD**
  - Encourage period of euthymia
  - Sustained remission: May consider tapering and discontinuing
  - More recently depressed or with symptoms: Consider remaining on medication, optimizing medication
- **Pregnant women with severe MDD**: Medication is first-line
- **Pregnant women on antidepressants during pregnancy**: Take into account patient preferences, previous course of illness
- Medication selection should be based on known safety information

APA = American Psychiatric Association; ACOG = American College of Obstetricians and Gynecologists; MDD = major depressive disorder.

Yonkers KA, et al. *Obstet Gynecol*. 2009;114(3):703-713.

Antidepressants and Pregnancy:
Overview and Controversies

Massachusetts General Hospital. MGH Center for Women's Mental Health. www.womensmentalhealth.org. Accessed June 3, 2019.

SSRI Use during Pregnancy

- Prevalence of SSRI use during pregnancy is 3% to 7%
- Recent findings and more data inform the pharmacologic treatment of depression during pregnancy
  - Consistent conclusions that the *absolute* risk of SSRI exposure in pregnancy is small
  - Recent case-control studies reveal inconsistent data regarding teratogenic risk of individual SSRIs
- Reproductive safety data on SSRI exceed what is known about most other medicines used in pregnancy

SSRI = selective serotonin reuptake inhibitor.

Louik C, et al. *N Engl J Med*. 2007;356(26):2675-2683. Einarson TR, et al. *Pharmacoepidemiol Drug Saf*. 2005;14(12):823-827. Einarson A, et al. *Am J Psychiatry*. 2008;165(6):749-752. Alwan S, et al. *N Engl J Med*. 2007;356(26):2684-2692. Greene MF. *N Engl J Med*. 2007;356(26):2732-2733. Hallberg P, et al. *J Clin Psychopharmacol*. 2005;25(1):59-73. Wogelius P, et al. *Epidemiology*. 2006;17(6):701-714. Pedersen LH, et al. *BMJ*. 2009;339:b3569.

Cardiovascular Malformations?

Results

- 19 studies were above quality threshold and make up the primary meta-analyses
- Pooled RRs were derived by using random-effects methods. Antidepressant exposure was not associated with
  - congenital malformations (RR=.93; 95% CI, 0.85–1.02; *P*=.113) or
  - major malformations (RR=1.07; 95% CI, 0.99–1.17; *P*=.095)
- However, increased risk for
  - cardiovascular malformations (RR=1.36; 95% CI, 1.08–1.71; *P*=.008) and
  - septal heart defects (RR=1.40; 95% CI, 1.10–1.77; *P*=.005) were found;
  - the RR for ventral septal defects was similar to septal defects, although not significant (RR=1.54; 95% CI, 0.71–3.33; *P*=.274)
- Pooled effects were significant for paroxetine and cardiovascular malformations (RR=1.43; 95% CI, 1.08–1.88; *P*=.012)
- These results are contrasted with those addressing methodological limitations but are typically consistent

RR = relative risk.

Grigoriadis S, et al. *J Clin Psychiatry*. 2013;74(4):e293-e308.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Antidepressant Use in Pregnancy and the Risk of Cardiac Defects

Krista F. Huybrechts, Ph.D., Kristin Palmsten, Sc.D., Jerry Avorn, M.D., Lee S. Cohen, M.D., Lewis B. Holmes, M.D., Jessica M. Franklin, Ph.D., Helen Mogun, M.S., Raisa Levin, M.S., Mary Kowal, B.A., Soko Setoguchi, M.D., Dr.P.H., and Sonia Hernández-Díaz, M.D., Dr.P.H.

N ENGL J MED 370;25 NEJM.ORG JUNE 19, 2014

- No evidence of increased risk for major malformations or cardiovascular malformations in children of pregnant women exposed to SSRIs

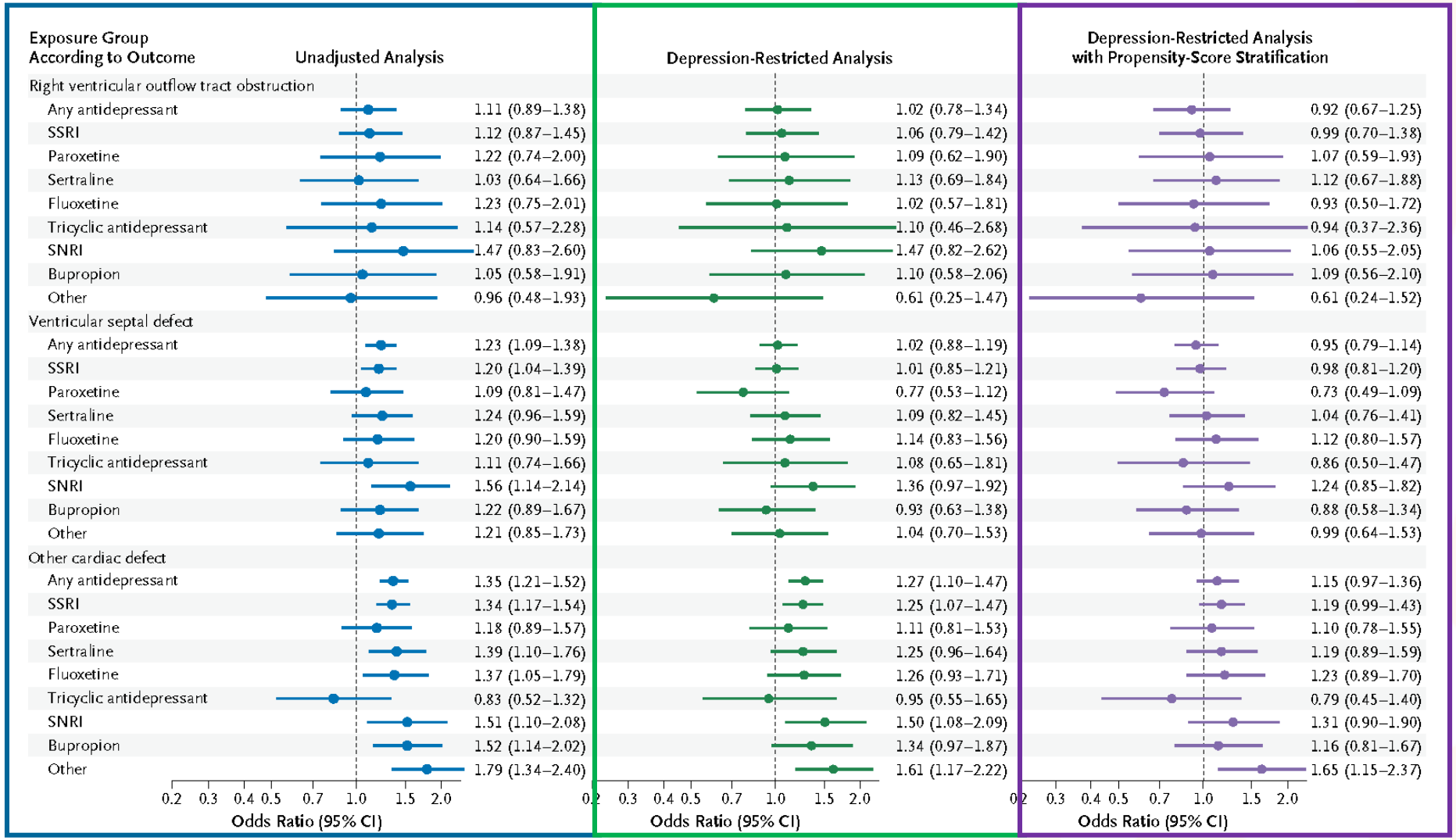
Huybrechts KF, et al. *N Engl J Med*. 2014;370(25):2397-2407.

Risk of Cardiovascular Malformation following SSRI Exposure

- Analysis of 949,504 pregnant women enrolled in Medicaid
  - 3 months prior to pregnancy to 1 month following pregnancy
- 6.8% use of SSRIs during first trimester
- Risk for cardiac defects attenuated with increasing levels of adjustment for confounding

Huybrechts KF, et al. *N Engl J Med*. 2014;370(25):2397-2407.

Cardiovascular Malformation and Fetal SSRI Exposure



Huybrechts KF, et al. *N Engl J Med*. 2014;370(25):2397-2407.

Are SSRIs Associated with an Increased Risk of Autism?

Studies have been inconsistent; those that best account for confounding variables do not show associations

1) **Canadian Study**: Health administrative data sets; factored in large number of potential confounders and compared exposed children with unexposed siblings
   - 35,906 singleton births: After factoring in propensity scores for confounding, **association not significant**; association also not significant when exposed children were compared with unexposed siblings
2) **Swedish Study**: Controlled for pregnancy, maternal and paternal covariates, sibling comparisons, timing of exposure
   - Offspring born to 943,776 mothers
   - First trimester exposure associated **with a small increased risk of preterm birth, but no increased risk of small for gestational age, autism spectrum disorder, or ADHD**

ADHD = attention-deficit/hyperactivity disorder

Brown HK, et al. *JAMA*. 2017;317(15):1544-1552. Sujan AC, et al. *JAMA*. 2017;317(15):1553-1562.

Antidepressants during Pregnancy:
Later Pregnancy Considerations

- Risk of persistent pulmonary hypertension of newborn with SSRIs?

- Inconsistent results
  - 1 report showed increased risk by 6-fold (approximately 1%)
  - Lower association seen (0.15%)
  - No association seen

Chambers CD, et al. *N Engl J Med*. 2006;354(6):579-587. Källén B, et al. *Pharmacoepidemiol Drug Saf*. 2008;17(8):801-806. Andrade SE, et al. *Pharmacoepidemiol Drug Saf*. 2009;18(3):246-252. Wichman CL, et al. *Mayo Clin Proc*. 2009;84(1):23-27. Wilson KL, et al. *Am J Perinatol*. 2011;28(1):19-24.

Antidepressant Use Late in Pregnancy and Risk of PPHN

- **Large Medicaid Database – 3.8 million pregnancies**
  - 128,950 women (3.4%) filled at least 1 prescription for antidepressants last 90 days of pregnancy; 2.7% used an SSRI and 0.7% used a non-SSRI
  - Overall, 7630 infants not exposed to antidepressants were diagnosed with PPHN (20.8; 95% CI, 20.4–21.3 per 10,000 births) compared with 322 infants exposed to SSRIs (31.5; 95% CI, 28.3–35.2 per 10,000 births), and 78 infants exposed to non-SSRIs (29.1; 95% CI, 23.3–36.4 per 10,000 births)
- **Absolute Risks**
  - With SSRI: 31.5/10,000 = **0.3%**
  - No antidepressant: 20.8/10,000 = **0.2%**
- Associations between antidepressant use and PPHN were attenuated with increasing levels of confounding adjustment

PPHN = persistent pulmonary hypertension.
Huybrechts KF, et al. *JAMA*. 2015;313(21):2142-2151.

Antidepressants during Pregnancy: *Later Pregnancy Considerations*

- Reports of suspected neonatal syndrome: “withdrawal” or “toxicity,” complications after *in utero* exposure to SSRIs; low birth weight; prematurity
- Overall, studies do not adequately control for maternal mental health condition, adequate blinding of exposure in neonatal assessments
- Tapering does not appear to decrease occurrence when confounders assessed

Suri R, et al. *Am J Psychiatry*. 2007;164(8):1206-1213. Moses-Kolko EL, et al. *JAMA*. 2005;293(19):2372-2383. Jordan AE, et al. *J Matern Fetal Neonatal Med*. 2008;21(10):745-751. Oberlander TF, et al. *Arch Gen Psychiatry*. 2006;63(8):898-906. Warburton W, et al. *Acta Psychiatr Scand*. 2010;121(6):471-479.

Bupropion and Pregnancy

- **Bupropion Pregnancy Registry**, prospective birth outcome data
  - 3.6% (24/675) of the cohort experienced a congenital anomaly after first trimester exposure
  - There was no clear pattern of type of birth defects
- Small prospective study N=136 women who used bupropion in the first trimester, there was no evidence of increased rates of malformations compared with 2 groups of women, those who used other antidepressants and those who had known nonteratogenic exposures
- Small but increased risk of cardiovascular left outflow defects was reported in a retrospective case control study from a birth defect registry
  - The absolute risk was approximately 2/1000 pregnancies

The Bupropion Pregnancy Registry. http://pregnancyregistry.gsk.com/documents/bup_report_final_2008.pdf. Accessed June 3, 2019. Chun-Fai-Chan B, et al. *Am J Obstet Gynecol*. 2005;192(3):932-936. Cole JA, et al. *Pharmacoepidemiol Drug Saf*. 2007;16(5):474-484. Alwan S, et al. *Am J Obstet Gynecol*. 2010;203(1):52.e1-52.e6.

Risk of Relapse for MDD during Pregnancy

- Prospective study of MDD during pregnancy: N=201; euthymic prior to pregnancy, currently/recently using antidepressants; patients decided to continue/discontinue medication (not randomized)
- **43% relapsed during pregnancy**
  - 26% of those who continued medication
  - **68% of those who discontinued medication**
- Predictors of relapse
  - Unmarried; younger (< 32 years); more recurrent depression, earlier onset of depression

Cohen LS, et al. *JAMA*. 2006;295(5):499-507.

Postpartum Mood Disorders

- Postpartum blues
- Postpartum depression
- *DSM-5*: Peripartum onset specifier
  - Onset within 4 weeks of delivery, debatable
- Postpartum psychosis
- Considerations for bipolar disorder

Postpartum Depression

- Prevalence: 10% to 15%
- Anxiety is common
- Risks of untreated maternal depression
- Risks of medication exposure via breast milk

Nonacs R, et al. *J Clin Psychiatry*. 1998;59 Suppl 2:34-40.

Negative Effects of Maternal Depression on the Child

- Insecure attachment
- Behavioral problems
- Cognitive function
- Increased risk of abuse, neglect
- Childhood psychiatric diagnoses and symptoms
- Adherence with preventive measures
- Thoughts of harming infant

Civic D, et al. *Matern Child Health J*. 2000;4(4):215-221. Cicchetti D, et al. *Dev Psychopathol*. 1998;10(2):283-300. Feldman R, et al. *J Child Psychol Psychiatry*. 1999;40(6):929-939. Murray L, et al. *J Child Psychol Psychiatry*. 1999;40(8):1259-1271. Murray L, et al. *J Child Psychol Psychiatry*. 1996;37(8):927-935. Sharp D, et al. *J Child Psychol Psychiatry*. 1995;36(8):1315-1336. Kotch JB, et al. *Child Abuse Negl*. 1999;23(4):305-319. Cadzow SP, et al. *Child Abuse Negl*. 1999;23(9):845-853. Jennings KD, et al. *J Affect Disord*. 1999;54(1-2):21-28. McLennan JD, et al. *Pediatrics*. 2000;105(5):1090-1095. Weissman MM, et al. *Am J Psychiatry*. 2006;163(6):1001-1008.

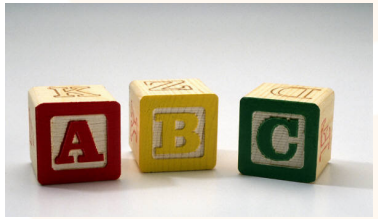
Breastfeeding

- …The experience of breastfeeding is special for so many reasons – the joyful bonding with your baby, the cost savings, and the health benefits for both mother and baby…
  - www.womenshealth.gov/breastfeeding/why-breastfeeding-is-important/index.html
- …Time to declare an end to the breastfeeding dictatorship that is drowning women in guilt and worry just when they most need support...

Lemmon GT. Breastfeeding is a Choice, Let's Treat it that Way. May 11, 2012. www.huffingtonpost.com/gayle-tzemach/breastfeeding_b_1509658.html. Accessed June 3, 2019.

Treatment Recommendations:
Perinatal Depression

- Moderate-to-severe depression
  - Consider role of antidepressants; discuss risks and benefits with mother
- Use lowest effective doses
- Consultation with experts
- Maximize non-medication alternatives



Trials of Antidepressants for Postpartum Depression

Study	Design and Size	Medication Studied, Result
Appleby et al, 1997	Placebo-controlled, N=87; CBT studied in same trial	Fluoxetine – superior to placebo
Yonkers et al, 2008	Placebo controlled, N=70	Paroxetine – not superior to placebo
Wisner et al, 2006	RCT, sertraline vs nortriptyline, N=109	Sertraline vs nortriptyline – no significant difference
Hantsoo et al, 2013	Placebo-controlled RCT, N=36	Sertraline – superior to placebo
Bloch et al, 2012	N=40, all received brief psychodynamic therapy, RCT to sertraline or placebo	Both groups improved – no significant difference for sertraline vs placebo
Sharp et al, 2010	RCT, antidepressant selected by general practitioner or counseling, N=254	Antidepressants – superior to placebo
Misri et al, 2012	Open trial, N=15	Citalopram – open study
Misri et al, 2004	N=35, all received paroxetine, half randomized to CBT also	Paroxetine – no control group
Stowe et al, 1995	Open-label; N=21	Sertraline – open study
Cohen et al, 1997	Open-label; N=19	Venlafaxine – open study
Suri et al, 2001	Open-label; N=6	Fluvoxamine – open study
Nonacs et al, 2005	Open-label; N=8	Bupropion – open study

CBT = cognitive-behavioral therapy; RCT = randomized controlled trial.

Appleby L, et al. *BMJ*. 1997;314(7085):932-936. Yonkers KA, et al. *J Clin Psychiatry*. 2008;69(4):659-665. Bloch M, et al. *J Clin Psychiatry*. 2012;73(2):235-241. Wisner KL, et al. *J Clin Psychopharmacol*. 2006;26(4):353-360. Misri S, et al. *J Clin Psychiatry*. 2004;65(9):1236-1241. Stowe ZN. *Depression*. 1995;3(1-2):49-55. Cohen LS, et al. *J Clin Psychiatry*. 2001;62(8):592-596. Suri R, et al. *Am J Psychiatry*. 2001;158(10):1739-1740. Nonacs RM, et al. *Int J Neuropsychopharmacol*. 2005;8(3):445-449. Kim DR, et al. *Expert Opin Pharmacother*. 2014;15(9):1223-1234.

Breastfeeding and Antidepressants

- Most studies of infant exposure to antidepressants show low levels of drug in breast milk and infant serum

Fluoxetine	Due to long half-life, may be more likely to be found at detectable levels in infant serum, especially at higher doses. Reasonable for use if a woman has had a good previous response to it and reasonable to consider if used during pregnancy
Sertraline	Consistent reports of low levels of exposure, relatively large amount of study
Citalopram, escitalopram	Less systematic study of mom–baby pairs compared with sertraline and paroxetine, observed low levels of exposure to infant via breastfeeding
Paroxetine	Consistent reports of low levels of exposure, relatively large amount of study. Use limited by commonly experienced withdrawal symptoms, may be more sedating than other SSRIs
Bupropion	Paucity of systematic studies; a few case reports in older infants that demonstrate low levels of exposure via breastfeeding. May be advantageous in smokers. Reasonable for use if women have had good previous response. One case report of possible infant seizure
Venlafaxine, desmethyl-venlafaxine	Higher levels of desmethylvenlafaxine found in breast milk than venlafaxine. No adverse events reported
TCAs	Considered reasonable for breastfeeding if use clinically warranted; few adverse effects in babies and generally low levels of exposure reported
Mirtazapine, nefazodone, MAOIs, duloxetine	Systematic human lacking in the context of breastfeeding

MAOI = monoamine oxidase inhibitor; TCA = tricyclic antidepressant.

Weissman AM, et al. *Am J Psychiatry*. 2004;161(6):1066-1078. Burt VK, et al. *Am J Psychiatry*. 2001;158(7):1001-1009.

Perinatal Depression

- Non-medication treatments
  - **Psychotherapy**
  - Electroconvulsive therapy
  - CAM treatments (Integrative Medicine)

CAM = Complementary and Alternative Medicine.

Spinelli MG. *Am J Psychiatry*. 1997;154(7):1028-1030. Dennis CL. *J Clin Psychiatry*. 2004;65(9):1252-1265. Yonkers KA, et al. *Obstet Gynecol*. 2009;114(3):703-713. Miller LJ. *Hosp Community Psychiatry*. 1994;45(5):444-450.

CAM/Integrative Treatments

- Omega-3 fatty acids—add-on
- Exercise—add-on
- Folate—add-on
- SAMe—?monotherapy (no specific study)
- St. John's wort—similar to antidepressants, but less known
- Acupuncture—monotherapy or add-on
- Bright light therapy—monotherapy or add-on
- Massage—add-on

SAMe = S-adenosylmethionine.

Parker G, et al. *Am J Psychiatry*. 2006;163(6):969-978. Freeman MP, et al. *Acta Neuropsychiatrica*. 2006;18, 21-24. Su KP, et al. *J Clin Psychiatry*. 2008;69(4):644-651. Nemets B, et al. *Am J Psychiatry*. 2002;159(3):477-479. Deligiannidis KM, et al. *Psychiatr Clin North Am*. 2010;33(2):441-463.

Brexanolone

- FDA approval in 2019
- IV delivered analogue of allopregnanolone
- Allosteric modulator of GABA receptors
- 2 positive, controlled trials in postpartum depression (onset during late pregnancy or postpartum, presented within 6 months postpartum with MDD)
- Rapid onset of benefit, durable efficacy to 30 days
- Implementation challenges: Cost, in hospital

GABA = gamma-aminobutyric acid.

Meltzer-Brody S, et al. *Lancet*. 2018;392(10152):1058-1070.

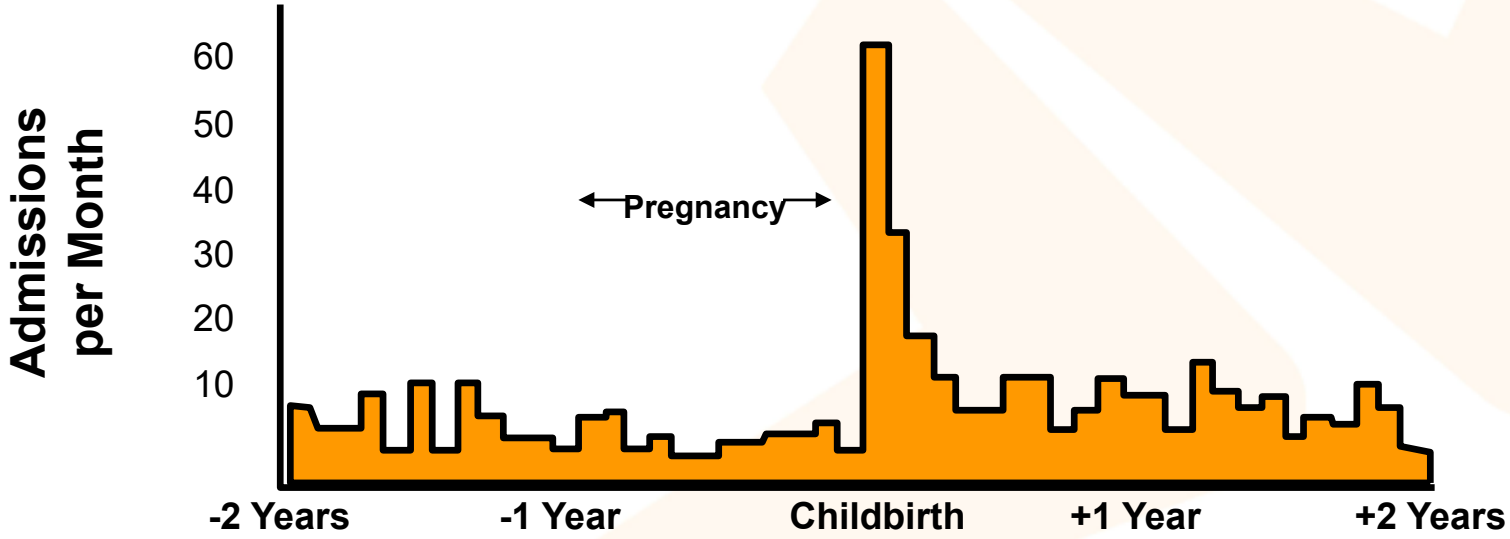
Bipolar Disorder in Pregnancy and Postpartum

Pregnancy and Postpartum:
Risks of Discontinuing Medication

- Retrospective and prospective data show mean rates of relapse during pregnancy between 55% to 70%
- Women who discontinue medication more likely to experience recurrences (85.5% vs 37%) and spend more time ill
- Particularly high rate of mood episodes postpartum (70%)
- Recurrence risk greater after rapid discontinuation (≤ 2 weeks) than gradual (2 to 4 weeks)
- Unplanned pregnancy associated with greater risk of recurrence

Viguera AC, et al. *Am J Psychiatry*. 2000;157(2):179-184. Viguera AC, et al. *Am J Psychiatry*. 2007;164(12):1817-1824.

Risk of Psychiatric Hospitalization during Pregnancy and Postpartum



Highest risk of hospitalization for new mothers is 10 to 19 days postpartum, increased outpatient contacts first 3 months

Kendell RE, et al. *Br J Psychiatry*. 1987;150:662-173. Munk-Olsen T, et al. *JAMA*. 2006;296(21):2582-2589.

Postpartum Psychosis

Postpartum Psychosis

- 1 to 2 per 1000 pregnancies
- Rapid, dramatic onset within first 2 weeks
- **High risk of harm to self and infant**
- **Suspect bipolar disorder**
  - Underlying diagnosis: Affective psychosis (bipolar disorder or schizoaffective disorder)
  - Family and genetic studies, index episode follow-up

Nonacs R, et al. *J Clin Psychiatry*. 1998;59 Suppl 2:34-40. Jones I, et al. *Ann Med*. 2001;33(4):248-256. Spinelli MG. *Am J Psychiatry*. 2009;166(4):405-408.

Postpartum Psychosis (cont'd)

- Psychiatric emergency
- Estimated that 4% of women with postpartum psychosis commit infanticide
  - Actual rates of infanticide are difficult to estimate, as infanticide may be underreported

Spinelli MG. *Am J Psychiatry*. 2004;161(9):1548-1557. Spinelli MG. *Am J Psychiatry*. 2009;166(4):405-408.

Differentiating OCD and Psychosis

Postpartum OCD

- Thoughts are ego-dystonic
- Disturbed by thoughts
- Avoid objects or being with their newborn
- Very common disorder
- Low risk of harm to baby

Postpartum Psychosis

- Thoughts are ego-syntonic
- Rarely distressed by thoughts
- Do not have avoidant behaviors
- Not common disorder
- High risk of harm to baby

OCD = obsessive-compulsive disorder.

Brandes M, et al. *Arch Womens Ment Health*. 2004;7(2):99-110.

Mood Stabilizers in Pregnancy

- Lithium: First-trimester risk of cardiovascular malformations
  - Ebstein's anomaly: 0.1% to 0.2% (RR=10–20)
  - RR for cardiac malformations is 1.2 to 7.7 and the risk for Ebstein's anomaly rises from 1/20,000 to 1/1000
- Lithium
  - Complicated by maternal GFR changes during pregnancy. Excreted more rapidly—may need to increase dose
  - After delivery, GFR decreases rapidly, should follow lithium levels during labor and delivery, adjust dose as needed

RR = risk ratio; GFR = glomerular filtration rate.

Yonkers KA, et al. *Am J Psychiatry*. 2004;161(4):608-620. Newport DJ, et al. *Am J Psychiatry*. 2005;162(11):2162-2170.

Valproic Acid

- **WORST TERATOGEN KNOWN AMONG PSYCHOTROPICS**
- Rate of major malformations: ≥ 10%
  - Neural tube defects, craniofacial, cardiovascular, and others
  - Risk of defects is substantial in very early pregnancy
- Associated with increased risk for adverse cognitive and neurodevelopmental effects
  - Long-term follow-up (up to 3 years) suggests fetal exposure to valproate associated with lower IQ scores (not observed with lamotrigine)

Yonkers KA, et al. *Am J Psychiatry*. 2004;161(4):608-620. Newport DJ, et al. *Am J Psychiatry*. 2005;162(11):2162-2170. Meador KJ, et al. *Epilepsy Behav*. 2009;15(3):339-343.

IQ Scores of Children at 3 Years of Age According to *In Utero* Exposure to Antiepileptic Drugs

Variable	Carbamazepine (N=73)	Lamotrigine (N=84)	Phenytoin (N=48)	Valproate (N=53)
Mean IQ (95% CI)†	98 (95–102)	101 (98–104)	99 (94–104)	92 (88–97)
Mean difference in IQ from valproate group (95% CI)‡	6 (0.6–12.0)	9 (3.1–14.6)	7 (0.2–14.0)	
P value§	0.04	0.009	0.04	

* The results are based on regression models for the intention-to-treat population (309 children). See Table 1 in the Supplementary Appendix for full results of the regression models. IQ at 3 years of age was imputed for 77 of the original 309 children born alive who were not assessed at that age (1 of these children died from severe heart malformation, 6 were enrolled in the NEAD study from the United Kingdom study after they had reached 3 years of age, 31 withdrew before 3 years of age, and 39 did not present for testing).

† Least-squares means from the primary analysis are given after adjustment for maternal IQ and age, antiepileptic-drug dose, infant's gestational age at birth, and maternal preconception use of folate.

‡ Although the confidence intervals for carbamazepine and phenytoin overlap with the confidence interval for valproate, the confidence intervals for the differences between carbamazepine and valproate and between phenytoin and valproate do not include zero.

§ P values are for the comparison with the valproate group. P values from tests of the null hypothesis of no difference from the valproate-group mean were adjusted for multiple comparisons.[23]

Meador KJ, et al. *N Engl J Med*. 2009;360(16):1597-1605.

Lamotrigine in Pregnancy

- Pregnancy increases lamotrigine clearance by > 50%
  - Returns to baseline after delivery
- Association with oral clefting—NOT seen with larger numbers
  - North American Antiepileptic Drug Pregnancy Registry; 5 of 564; first-trimester exposures rate of 8.9 per 1000, compared with 0.37 in general population
  - Recent large study of registries did not find any association between oral clefts and lamotrigine
- First-trimester birth defects more likely with anticonvulsant polypharmacy (International Lamotrigine Pregnancy Registry)
  - 3/168 (1.8%) with monotherapy; 5/50 (10%) lamotrigine + valproate

Myllynen PK, et al. *Eur J Clin Pharmacol*. 2003;58(10):677-682. Tran TA, et al. *Neurology*. 2002;59(2):251-255. Dolk H, et al. *Neurology*. 2008;71(10):714-722. Holmes LB, et al. *Neurology*. 2008;70(22 Pt 2):2152-2158. Hernández-Díaz S, et al. *Neurology*. 2012;78(21):1692-1699. Holmes LB, et al. *Arch Neurol*. 2011;68(10):1275-1281.

Atypical Antipsychotics in Pregnancy

- **Large administrative Medicaid database**
  - Nationwide sample of N=1,360,101 pregnant women
  - After confounding adjustment, the RR was reduced to 1.05 (95% CI, 0.96–1.16) for atypical APs and 0.90 (95% CI, 0.62–1.31) for typical APs. The findings for cardiac malformations were similar
  - For the individual agents examined, a small increased risk in overall malformations (RR, 1.26; 95% CI, 1.02–1.56) and cardiac malformations (RR, 1.26; 95% CI, 0.88–1.81) was found for risperidone that was independent of measured confounders
- **Pooled odds ratios of prospective studies**
  - AP exposure associated with slightly increased risk of major malformations, heart defects, preterm delivery, small-for-gestational-age births, decreased birth weight
  - There was no significant difference in the risk of major malformations differences between typical (and atypical) AP medications

AP = antipsychotic.

Huybrechts KF, et al. *JAMA Psychiatry*. 2016;73(9):938-946. Coughlin CG, et al. *Obstet Gynecol*. 2015;125(5):1224-1235.

National Pregnancy Registry for Atypical Antipsychotics

- Research study at the Massachusetts General Hospital Center for Women's Mental Health
- To determine the safety of atypical antipsychotics in pregnancy for women and their babies
- Participation will involve 3 brief phone interviews over approximately 8 months

Call toll-free:
1-866-961-2388

National Pregnancy Registry for Atypical Antipsychotics

- Now > 1500 patients have been enrolled!

Early Data

- As of December 2014, N=487 enrolled
- N=303 eligible for analyses; 89 controls
- Rates of major malformations in the 2 groups similar
  - 1.4% (3/214 live births) in exposed group
  - 1.1% (1/89) in the comparison group
  - Odds ratio for major malformations comparing exposed infants with unexposed infants was 1.25 (95% CI, 0.13–12.19) – not statistically significant

Quetiapine: N=152 exposure to quetiapine compared with 205 controls

- 2/155 malformations were confirmed (1.3%), compared with 3/210 (1.4%) in control group
- Odds ratio for major malformations between infants with and without quetiapine exposure was 0.90 (95% CI=0.15, 5.46), which is consistent with the pooled estimate of the available controlled data on fetal exposure to quetiapine

Cohen LS, et al. *Am J Psychiatry*. 2016;173(3):263-270. Cohen LS, et al. *Am J Psychiatry*. 2018;175(12):1225-1231.

Mood Stabilizers and Breastfeeding

- **Lithium**
  - Toxicity reported in cases with infant serum levels at 0.1 to 0.5× the maternal level
  - Contraindicated at one time by the American Academy of Pediatrics
    - Revised to classification “Drugs That Have Been Associated With Significant Effects on Some Nursing Infants and Should Be Given to Nursing Mothers With Caution”

American Academy of Pediatrics Committee on Drugs. *Pediatrics*. 2001;108(3):776-789.

Mood Stabilizers and Breastfeeding (cont'd)

Lithium and Breastfeeding

- N=10 mother–baby pairs
- Mothers stable, lithium monotherapy 600 to 1200 mg/day
- Babies' serum levels 0.09 to 0.3 mEq/L (average 0.16)
- Transient increases in elevated infant TSH, BUN, Cr

Recommendations—Consider lithium when

1. Bipolar disorder in mother who is stable
2. Lithium monotherapy (or simple regimen)
3. Adherence to infant monitoring (lithium level, TSH, BUN, Cr immediately postpartum, 4 to 6 weeks of age, and then every 8 to 12 weeks)
4. Healthy infant
5. Collaborative pediatrician

BUN = blood urea nitrogen; Cr = creatinine; TSH = thyroid-stimulating hormone.

Viguera AC, et al. *Am J Psychiatry*. 2007;164(2):342-345.

Benzodiazepines/Hypnotics and Related Treatments

Sleep Medications and Pregnancy

- The majority of women experience sleep dysregulation during pregnancy
- Some may have impact on functioning
- Nonpharmacologic treatments are considered first-line
  - Sleep hygiene
  - CBT
- Important to treat the underlying conditions

Benzodiazepines and Pregnancy

- 3.9% of pregnant women in the United States receive treatment with a benzodiazepine or benzodiazepine-like medication
- More likely to receive other medications, higher BMI, older, smokers, using antidepressants than non-benzodiazepine users
- First trimester exposure: Inconsistent findings of association with cleft palate or other congenital abnormalities
  - **Recent studies do not suggest teratogenicity, including risk of oral clefting**
- Late pregnancy exposure: Possible withdrawal, neonatal sedation, hypotonia, cyanosis
- Avoidance in the first trimester, avoidance of polypharmacy ideal if possible

BMI = body mass index.

Kanto JH. *Drugs*. 1982;23(5):354-380. Hanley GE, et al. *BMC Pregnancy Childbirth*. 2014;14:242. Ornoy A, et al. *Reprod Toxicol*. 1998;12(5):511-515. Eros E, et al. *Eur J Obstet Gynecol Reprod Biol*. 2002;101(2):147-154. Whitelaw AG, et al. *Br Med J*. 1981;282(6270):1106-1108. Mazzi E. *Am J Obstet Gynecol*. 1977;129(5):586-587. Iqbal MM, et al. *Del Med J*. 2002;74(3):127-135. Askaa B, et al. *Obstet Gynecol Int*. 2014;2014:945621. Wikner BN, et al. *J Clin Psychopharmacol*. 2011;31(3):356-359. Eros E, et al. *Eur J Obstet Gynecol Reprod Biol*. 2002;101(2):147-154. Wikner BN, et al. *Pharmacoepidemiol Drug Saf*. 2007;16(11):1203-1210. Wikner BN, et al. *Pharmacoepidemiol Drug Saf*. 2007;16(9):988-994. Bellantuono C, et al. *Gen Hosp Psychiatry*. 2013;35(1):3-8. Okun ML, et al. *Am J Obstet Gynecol*. 2015;212(4):428-441. Grigoriadis S, et al. *J Clin Psychiatry*. 2018;79(5):pii: 17r12011.

Benzodiazepines and Pregnancy (cont'd)

- Recent study suggested association with Caesarean section, low birth weight, use of ventilator support for newborn
- Timing of exposure likely makes difference in obstetrical outcomes
- May contribute to poor neonatal adaptation syndrome when used with antidepressants
- Possible long-term impact on language development
- Difficult to disentangle confounding variables, disease state, concomitant medications

Yonkers KA, et al. *JAMA Psychiatry*. 2017;74(11):1145-1152. Salisbury AL, et al. *Am J Psychiatry*. 2016;173(2):147-157. Odsbu I, et al. *Eur J Clin Pharmacol*. 2015;71(3):283-291.

Non-Benzodiazepine Hypnotics

- Much less studied than benzodiazepines
- Zolpidem
  - Largest study suggested increased association with obstetrical complications (low birth weight, preterm delivery)
  - No evidence of major malformations
- Class as a whole that has been studied does not appear to increase risk of teratogenicity, although there are few studies
  - Zopiclone, zolpidem, zaleplon do not appear to increase risk of major malformations

Wikner BN, et al. *J Clin Psychopharmacol*. 2011;31(3):356-359. Wang LH, et al. *Clin Pharmacol Ther*. 2010;88(3):369-374. Wikner BN, et al. *Pharmacoepidemiol Drug Saf*. 2007;16(11):1203-1210. Wikner BN, et al. *Pharmacoepidemiol Drug Saf*. 2007;16(9):988-994.

Other Sleep Treatments

- Melatonin
  - Should not assume safety; supplementation relatively unstudied in human pregnancy
- Sedating antihistamines
  - Recent large meta-analysis, review: Not associated with major malformations or adverse outcomes
  - FDA approved antihistamine compound for use in pregnancy: Doxylamine (FDA-approved for morning sickness: Diclegis®)

The use of these medications for this indication is off-label. Brand names are included in this slide for participant clarification purposes only. No product promotion should be inferred.

Etwel F, et al. *Drug Saf*. 2017;40(2):121-132. Gilboa SM, et al. *Expert Opin Drug Saf*. 2014;13(12):1667-1698.

Other Sleep Treatments (cont'd)

- TCAs—recent study suggested possible small increased risk of major malformations (facial/neck, odds ratio 1.16)
- Trazodone—limited data, reassuring but not definitive on lack of association with major malformations
- Mirtazapine—limited data, reassuring but not definitive on lack of association with major malformations

The use of these medications for this indication is off-label.

Bérard A, et al. *BMJ Open*. 2017;7(1):e013372. Einarson A, et al. *Can J Psychiatry*. 2003;48(2):106-110. Smit M, et al. *Eur Neuropsychopharmacol*. 2016;26(1):126-135.

ADHD and Treatment in Pregnancy and Breastfeeding

Women and Adult ADHD

- Growing appreciation that girls with ADHD have a substantial likelihood of continuing to have the disorder in adulthood
  - Biederman et al: Cohort of girls with longitudinal follow-up
    - Majority are still affected by ADHD over a decade later
    - Approximately one-third continuing to meet full criteria
    - Approximately another one-third meeting partial criteria
    - 10% experiencing impaired functioning

Kessler RC, et al. *Am J Psychiatry*. 2006;163(4):716-723. Brooks JS, et al. *Pediatrics*. 2013;131(1):5-13. Biederman J, et al. *Acta Psychiatr Scand*. 2012;125(2):147-156. Biederman J, et al. *Am J Psychiatry*. 2010;167(4):409-417.

Psychotherapies for ADHD

- CBT demonstrated to have a significant impact on symptoms
- CBT and “coaching” strategies can help improve functioning, assist in tailoring routines in ways to cope with ADHD
- For some women, such strategies may be adequate to sustain functioning during pregnancy

Mongia M, et al. *Curr Psychiatry Rep*. 2012;14(5):561-567. Vidal-Estrada R, et al. *Actas Esp Psiquiatr*. 2012;40(3):147-154. Parker DR, et al. *J Atten Disord*. 2013;17(3):215-232. Kubik JA. *J Atten Disord*. 2010;13(5):442-453.

Stimulants and Pregnancy

- Among women taking prescription stimulant medications, there have been findings of a small increased risk of preeclampsia and preterm birth
- Methylphenidate
    - Does not appear to increase the risk of overall major malformations
    - Possible small increased risk of cardiovascular malformations in large administrative database, not seen with amphetamines
        - Not seen in smaller prospective studies
    - May be associated with increased risk of hypertension in pregnancy

Cohen JM, et al. *Obstet Gynecol*. 2017;130(6):1192-1201. Huybrechts KF, et al. *JAMA Psychiatry*. 2018;75(2):167-175. Newport DJ, et al. *J Clin Psychiatry*. 2016;77(11):1538-1545. Diav-Citrin O, et al. *J Clin Psychiatry*. 2016;77(9):1176-1181.

Stimulants and Breastfeeding

- Generally documented as secreted in small amounts in milk
- Avoid if possible if not clinically necessary
- Not specifically contraindicated
- Advisable to monitor infant sleep and growth

Hackett LP, et al. *Ann Pharmacother*. 2006;40(10):1890-1891. Ilett KF, et al. *Br J Clin Pharmacol*. 2007;63(3):371-375. Spigset O, et al. *Am J Psychiatry*. 2007;164(2):348. Schaefer C, et al (Eds). *Drugs During Pregnancy and Lactation: Treatment Options and Risk Assessment*. Third Edition. Academic Press; 2015.

Non-Stimulant ADHD Medications

- Atomoxetine, clonidine, guanfacine
  - Very limited data
- Bupropion: Has the most data of the non-stimulants

Perinatal Psychopharmacology: Summary

- Women, children, and families are impacted
- Effective, safe, accessible, and acceptable treatments are needed
- Treatment considerations involve risks of medications, risks of the untreated disorder
- Unknowns: Collaborative treatment decisions, patient preferences highly prioritized