Psychopharmacology for Perinatal Mood and Anxiety Disorders
From the 2014 Regional Integrative Mental Health Conference, presented by the American Psychiatric Association in joint sponsorship with the Indiana Psychiatric Society and the Kentucky Psychiatric Medical Association

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Prevalence: anxiety and depression affect 10% to 20% of pregnant women; may be associated with noncompliance with prenatal care, increased use of substances, decreased birth weight, decreased Apgar scores, dysregulation of hypothalamic-pituitary-adrenal axis in infant, and depression in offspring.

Postpartum blues: 65% to 80% of new mothers increasingly tearful, moody, or irritable due to sleep deprivation and hormonal fluctuations; symptoms often peak near onset of lactation; most women improve in 2 to 3 weeks.

Postpartum depression (PPD): affects 7% to 15% of mothers; ≥50% of women with bipolar disorder (BPD) experience exacerbation postpartum; ≈60% of women with PPD experience depression during pregnancy (and many were depressed before pregnancy); perinatal and postpartum anxiety may be more prevalent than PPD; risk for PPD 2% to 5% in women with no psychiatric history; risk factors include previous psychiatric diagnosis, depression during pregnancy, history of PPD, family history of PPD or BPD, current stressors (e.g., interpersonal violence, poverty), and history of premenstrual dysphoric disorder.

Screening instruments: Edinburgh Postnatal Depression Scale commonly used to screen for depression during pregnancy, PPD, and anxiety; score >12 considered abnormal; Patient Health Questionnaire-9 also used.

Consequences of PPD: include insecure attachment and difficult temperament in infant, and development of psychiatric illness later in life; most serious consequences include suicide and infanticide; symptoms of PPD and depression similar; sleep disturbance prominent; other symptoms include anxiety and worry, indifference toward infant, poor appetite, guilt, and doubts about motherhood.

Anxiety: prevalence of generalized anxiety disorder increased during pregnancy, but prevalence of panic disorder does not change.

Obsessive-compulsive disorder (OCD): prevalence increased postpartum but not during pregnancy; patients with history of OCD commonly experience postpartum relapse; new-onset OCD also possible; mother may have intrusive, terrifying thoughts about harming infant; psychosis should be ruled out.

Bipolar disorder (BPD): antepartum — relapse of depression more common than relapse of mania; Viguer et al (2007) — studied possible destabilizing effect of pregnancy in women with history of BPD; found that rate of relapse in women taken off medications higher than that in women who continued taking medications; study criticized because many participants had history of resistance to treatment; recent studies — have found indications of stabilizing effect of pregnancy in some women; outcomes — infants fare poorly regardless of whether mother treated; may include low birth weight and microcephaly; postpartum — failure to treat associated with high risk for relapse of mania or depression; incidence of postpartum hypomania 18-fold higher in women with major depressive disorder (MDD) than in general population; onset of symptoms often abrupt; condition of women with postpartum blues worsens gradually, but women with BPD often experience onset of depression within 1st 2 wk or develop hypomania or mania within 1st 3 wk; mania — 40% to 80% of patients with BPD type I have postpartum mania; risk highest within 1st 2 wk; irritability and restlessness more common than elation or grandiosity; emergent treatment needed; conversion to psychosis common.

Postpartum psychosis (PPP): most psychiatrists view PPP as manifestation of underlying BPD (manic episode that quickly escalates to psychosis); others believe PPP distinct clinical entity because some women affected only during postpartum period; may present in first few days postpartum; escalates quickly; manifestations include delirium, hallucinations, and paranoia; 10% to 20% of women with BPD develop PPP; 10% of women with history of any psychiatric admission experience PPP after first birth; among women hospitalized during pregnancy for BPD or psychosis, >40% require readmission postpartum; 90% of PPP and postpartum BPD occur in 1st month; management — most patients require hospitalization; organic causes should be ruled out, including stroke, thyrotoxicosis, urea cycle defect, lupus cerebritis, infection, metabolic disorder, and drugs; starting lithium immediately after birth highly effective in patients with history of PPP.

Medications: may affect fetus, but consequences of abrupt discontinuation may be worse and not recommended in newly pregnant women (fetus already exposed); need for medication influenced by severity of disorder and previous negative reaction to stopping medication.

Nonpharmacologic management: preferred; cognitive behavioral therapy and interpersonal therapy effective; light therapy investigational, but safe; acupuncture may be beneficial.

Educational Objectives
The goal of this program is to improve the diagnosis and treatment of perinatal mood and anxiety disorders. After hearing and assimilating this program, the clinician will be better able to:

1. Explain the typical course of bipolar disorder during pregnancy and postpartum.
2. Identify and manage postpartum psychosis.
3. Counsel a patient who may require an antidepressant during pregnancy but is concerned about possible effects on the fetus.
4. Choose an appropriate antidepressant for women who are breastfeeding.
5. Assess the risks of using first-generation and atypical antipsychotics during pregnancy and postpartum.

Faculty Disclosure
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omega-3 fatty acids recommended (ratio of eicosapentaenoic acid [EPA] to docosahexaenoic acid should be 2:1; recommended dose of EPA 1000 to 1500 mg); folic acid intake should be optimized (patients with mutation in molybdenum cofactor deficiency need supplements of L-5-methyltetrahydrofolate to prevent malformations)

Fetal risk associated with medication use: rate of major malformations during first trimester should be compared with baseline rate; behavioral teratogenicity may develop secondary to medication use in second and third trimesters; persistent pulmonary hypertension of newborn (PPHN) may develop; other considerations include effects of medication on duration of labor, fetal growth, and neural development including risk for future psychiatric illness

Quality of studies: until relatively recently, many studies based on retrospective analyses without systematic reporting, blinded assessments, or control of confounders; studies comparing treated patients with healthy patients do not control for severity of illness; recent studies have compared treated women with untreated women, but depression and treatment tended to covary

Comorbidities: in many studies, patients taking multiple drugs such as selective serotonin reuptake inhibitors (SSRIs), benzodiazepines including alprazolam (Xanax) and lorazepam (Ativan), acetaminophen and oxycodone (Oxycet, Percocet, Roxicet), and ondansetron (Zofran); patients may be using tobacco and/or alcohol; other confounders include advanced maternal or paternal age, prematurity, and operative delivery

Food and Drug Administration (FDA) categories: inadequate risk profiles — SSRIs not significantly associated with major malformations; studies suggesting increased cardiac septal defects unblinded; 2011 study — SSRIs not associated with major anomalies; incidence of cardiac defects slightly increased in fetuses exposed to fluoxetine and paroxetine, but few cases detected and power of study questionable; increased neural tube defects (NTDs) observed, but study did not control for confounding variables and findings not confirmed by others; comorbidities increased in women on SSRIs, including presence of chronic diseases and use of tobacco or psychiatric drugs; folic acid syndrome observed in 8 cases, but confounding variables not controlled for; maternal psychiatric illness not controlled for; >150 comparisons performed, which increased risk for type I error

Counseling patients on SSRIs: obstetrician should discuss possible increased risk for shortened gestation (by average of 0.5 wk), miscarriage in first trimester, and decreased birth weight (>30 g); infants may be small for gestational age

Postnatal adaptation syndrome (PAS): may be related to toxicity, withdrawal, or underlying maternal illness; occurs in 25% to 30% of infants exposed to antidepressants during second half of pregnancy; signs include irritability, hypertonia, jitteriness, and poor sleeping and feeding; usually does not require intensive care; resolves within 2 wk; incidence highest in patients treated with paroxetine, fluoxetine, venlafaxine, and probably duloxetine; tapering before delivery does not decrease incidence of PAS

Persistent pulmonary hypertension of newborn: failure of cardiopulmonary circulation in fetus to transition to postnatal environment; condition life threatening; infants develop tachypnea and cyanosis; requires oxygenation of extracorporeal membrane; baseline prevalence 0.2%; absolute risk 6 to 12 per 1000 exposed infants, but some studies report no increase in risk after controlling for race, obesity, method of delivery, diabetes, and other factors; meta-analysis reported slight increase in risk for PPHN after 20 wk, but confounders not controlled for

Autism: study that reported increased risk for autism spectrum disorder (ASD; 4.3% in first trimester and 2.2% in second and third trimesters) controlled for history of maternal psychiatric illness but not for psychiatric symptoms during pregnancy; another study found increased risk for ASD but did not control for alcohol use, drug use, paternal age, maternal illness, or heredity (odds ratio for ASD insignificant in women successfully treated with antidepressants; study found that risk for ASD attributed to medications alone only 0.6%); recent data from large Danish registry revealed no association between antidepressants and increased risk for ASD

Neurodevelopment: study of venlafaxine and SSRIs found that severity of depression, not drug use, predicted behavior of child (factors other than exposure to antidepressant predicted intelligence quotient [IQ] as well); most studies in systematic review showed no effect

Choice of medication: level of risk probably comparable among SSRIs; paroxetine in category D because of risk for cardiac malformations; level of risk among citalopram, escitalopram, and fluvoxamine probably equivalent; large body of data supports nonteratogenicity of SSRIs in first trimester

Other antidepressants: bupropion — placement in category C based on possible association with left ventricular outflow anomalies; level of risk considered equivalent to that of SSRIs; lowers seizure threshold; venlafaxine and duloxetine — data reassuring; these drugs may be associated with miscarriage and neonatal symptoms, so SSRIs preferred; mirtazapine and trazadone — data sparse but reassuring; vilazodone, levomilnacipran (Fetzima), and vortioxetine (Brintellix) — no data available; tricyclic antidepressants — probably safe, but studies not well designed

Lactation: risk of exposure to medication through breast milk lower than that through transplacental passage; medications beneficial during pregnancy should not be changed postpartum; sertraline, paroxetine, and nortriptyline secreted in breast milk at lowest levels (studies have shown that receptor activation in infants occurs even when levels in milk undetectable); studies show no adverse risk associated with exposure through breast milk

Mood stabilizers: divalproex (Depakote) and valproic acid (Valproate) — should not be used during pregnancy because of increased risks for NTDs and other defects, autism, low IQ, and neonatal side effects; supplemental high-dose folate recommended in patients who require valproic acid; carbamazepine — safer than valproic acid; topiramate — in category D because of association with oral clefts, hypospadias, and preterm birth; lamotrigine (Lamictal) — may increase risk for oral clefts (to 2.5 per 1000) and carries warning from FDA; preferred by speaker (well tolerated, effective in small doses, and safe during breastfeeding); lithium — less strongly associated with Ebstein anomaly than previously believed, but incidence still high compared with controls (1 in 1000 vs 1 in 20,000); may be stopped 1 to 2 days before delivery to lessen neonatal hypotonia and improve feeding and sleeping; avoid use during period of cardiac formation; echocardiography recommended for fetuses exposed to lithium; difficult to manage during breastfeeding and may concentrate in milk, with resulting vomiting, diarrhea, and fever; frequent maternal blood testing needed; summary — most mood stabilizers increase risk for malformation; lamotrigine considered safest; lithium has no effect on growth or development of fetus after cardiac formation completed

Antipsychotics
First generation: few data available; agents with increased potency may lower risk for hypotension and placental hypoperfusion, however, low-potency agents commonly used for hyperemesis gravidarum; neonatal extrapyramidal symptoms
(EPS) may require several months to resolve; FDA issued warning but recognized that studies included women on multiple psychotropic agents; two studies have found negative effect on neural development (particularly reduced motor skills), but babies normalized by 12 mo of age (studies included women on multiple drugs)

Atypical: quetiapine (Seroquel), olanzapine, and risperidone (Risperdal) have received most study; ziprasidone associated with embryotoxicity in animal studies; effects of aripiprazole on humans not well studied; human data for lurasidone not available; placental passage ratio highest for olanzapine (ratio for quetiapine comparatively low)

Study: looked at atypical antipsychotics vs first-generation drugs vs no treatment; groups receiving treatment had higher body mass index, used more tobacco and drugs, used less folate and prenatal vitamins, and often on polytherapy; conclusions — first-generation antipsychotics associated with neonatal EPS, preterm birth, and low birth weight; atypical antipsychotics associated with large-for-gestational-age infants, weight gain, and gestational diabetes; atypical antipsychotics often preferred over mood stabilizers during pregnancy and postpartum, but risks for weight gain and sedation limit their use

Lactation: olanzapine associated with increased neonatal EPS; quetiapine and risperidone safe and not highly excreted in milk; other atypical antipsychotics not well studied

Benzodiazepines: no increase in malformations observed in >1 million births, but risk for oral cleft doubled in case-control studies; lorazepam and clonazepam not found to be associated with malformations (these drugs preferred over other benzodiazepines during pregnancy); occasional use of benzodiazepines reasonable, but daily use may cause neonatal withdrawal and decreased heart response in fetus; lorazepam (Ativan) and clonazepam (Klonopin) may be used during lactation; combining SSRI with benzodiazepine may increase risk for adverse events

Acknowledgments

Dr. Ricke was recorded at the 2014 Regional Integrated Mental Health Conference, held April 11-13, 2014, in West Baden Springs, IN, and presented by the American Psychiatric Association in joint sponsorship with the Indiana Psychiatric Society and the Kentucky Psychiatric Medical Association. For information, visit pdallc.com. The Audio Digest Foundation thanks Dr. Ricke and the sponsors for their cooperation in the production of this program.

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- Review Educational Objectives on page 1: 5 minutes
- Take pretest: 10 minutes
- Listen to audio program: 60 minutes
- Review written summary and suggested readings: 35 minutes
- Take posttest: 10 minutes

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PSYCHOPHARMACOLOGY FOR PERINATAL MOOD AND ANXIETY DISORDERS

To test online, go to www.audiodigest.org and sign in to online services. To submit a test form by mail or fax, complete Pretest section before listening and Posttest section after listening.

1. Which of the following statements about bipolar disorder (BPD) in pregnancy is true?
   (A) Relapse of mania is more common than relapse of depression during pregnancy
   (B) Pregnancy usually destabilizes patients with BPD
   (C) BPD is associated with microcephaly
   (D) Children of mothers treated for BPD have better outcomes than children of untreated mothers

2. All the following should be performed in the routine management of a patient with postpartum psychosis, except:
   (A) Treat with lithium
   (B) Test for thyrotoxicosis
   (C) Terminate breastfeeding
   (D) Hospitalize the patient

3. Lithium has been placed in pregnancy category ______ by the Food and Drug Administration.
   (A) B  (B) C  (C) D  (D) X

4. Postnatal adaptation syndrome is primarily associated with:
   (A) Selective serotonin reuptake inhibitors (SSRIs)
   (B) Benzodiazepines
   (C) Mood stabilizers
   (D) First-generation antipsychotics

5. A study that examined neurodevelopment in children exposed to venlafaxine in utero found that the drug was associated with:
   (A) Decreased intelligence
   (B) Adverse effects on childhood behavior
   (C) Persistent pulmonary hypertension
   (D) No effect

6. Which of the following SSRIs has been placed in category D because of a possible risk for cardiac malformations?
   (A) Citalopram
   (B) Escitalopram
   (C) Fluvoxamine
   (D) Paroxetine

7. Which of the following drugs lowers the seizure threshold?
   (A) Bupropion
   (B) Levomilnacipran
   (C) Mirtazapine
   (D) Sertraline

8. Which of the following mood stabilizers has been placed in category D because of associations with oral clefts, hypospadias, and preterm birth?
   (A) Lamotrigine
   (B) Topiramate
   (C) Divalproex
   (D) Lithium

9. Use of atypical antipsychotics during pregnancy is limited by which of the following side effects?
   1. Weight gain
   2. Sedation
   3. Preterm birth
   4. Extrapyramidal symptoms
      (A) 1,2
      (B) 1,2,3,4
      (C) 1,4
      (D) 2,3

10. Which of the following benzodiazepines have not been found to be associated with malformations and are preferred during pregnancy?
    1. Clonazepam
    2. Alprazolam
    3. Lorazepam
    4. Flurazepam
       (A) 1,2
       (B) 2,3
       (C) 1,3
       (D) 2,4

Answers to Audio Digest Obstetrics/Gynecology Volume 62, Issue 12: 1-D, 2-C, 3-C, 4-A, 5-A, 6-B, 7-C, 8-B, 9-D, 10-B

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