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Perinatal Depression: The Role of Reproductive Hormones and Hormone Manipulation in the Understanding and Treatment of Affective Dysregulation

David R. Rubinow, MD

University of North Carolina at Chapel Hill Chapel Hill, NC



Learning Objective

Recognize the symptoms and causes of perinatal depression.



Learning 2 Objective

Assess the role of reproductive hormones and hormone manipulation in the treatment of affective dysregulation.



What are Perinatal Mood Disorders?

- One of the family of Reproductive Endocrine-related Mood Disorders
- How common are PND?
- How are PND defined
 - Timing both before and after delivery
 - Symptoms
- What are risk factors for PND?
- What causes PND?

PND = Perinatal mood disorder.

Perinatal Depression: Background

COMMON

- 10%-15% prevalence
- 4 million women give birth annually in U.S.; one-half million with perinatal depressive disorder
- Most common, unrecognized complication of perinatal period
 - Compare to the prevalence rate of gestational diabetes at 2%-5%

MORBID

- Devastating consequences for patient and family
 - Low maternal weight gain, preterm birth
 - Impaired bonding between mother and infant
 - Increased risk of suicide and infanticide

MISSED

- No practice guidelines or routine screening
- Symptoms often different from "classic DSM-IV depression"

Meltzer-Brody S, et al. Arch Womens Ment Health. 2013;16(6):465-473.; Meltzer-Brody S, et al. Nat Rev Dis Primers. 2018;4:18022.; Meltzer-Brody S, Stuebe, A. Best Pract Res Clin Obstet Gynecol. 2014;28(1):49-60.

Perinatal Depression: Symptoms, Timing, Risk

• SYMPTOMS:

- Anxiety, agitation, irritability, panic; anger
- Feeling overwhelmed, can't care for baby, guilt, shame, inadequacy
- Impaired bonding
- Impaired concentration; hypervigilance about baby; intrusive thoughts

TIMING

- PREVALENCE STUDIES IN PREGNANCY, 0-4 WEEKS PP, AND > 4 WEEKS.
- NESDA: 43%, 34%, **23%, + 10%**
- Swedish Twin: 32%, 40%, 17% + 10%
 - Wisner: (27%), 33%, 40%

• RISK: THE PAST PREDICTS THE FUTURE

- Hx: Bipolar (20-50%); MDD (30%); Eating disorder (37%); PPP/fam hx of PPP (50%)
- Poor support, marital conflict; stressors; sleep disturbance
- Depression during pregnancy
- Obesity, substance abuse, adverse pregnancy/birth outcomes
- Trauma

Meltzer-Brody S, et al. Arch Womens Ment Health. 2013;16(6):465-473.; Viktorin A, et al. Am J Psychiatry. 2016;173(2):158-165.; Wisner KL, et al. JAMA Psychiatry. 2015;70(5):490-498.

Perinatal Depression: Elements of Assessment

- Psychiatric history
- Somatic comorbidities
- Mode of delivery/complications
- SI/HI (safety and harm)
- Bonding
- Baby feeding patterns
- PRESERVE SLEEP
- Metrics:
 - 1) EPDS Mild, Moderate, Severe (11, 15, 20/30)
 - 2) PHQ-9 Mild-moderate < 20, severe>20

Bergink V, et al. Am J Psychiatry. 2015; 172(2):115-123.

Cause of Perinatal Depression

- Is there any reason for thinking that PND is different from MDD?
- Is there a basis for thinking that steroids are involved in the precipitation of PND (i.e., do reproductive steroids regulate affective state)?

MDD = Major depressive disorder.



Metabolism Determines Actions: Testosterone











Estradiol Touches Virtually Every System Implicated in the Pathogenesis of Depression



Models of Depression

- Neurotransmitter deficiency
- Stress/CRH
- Neuroplasticity
- Cellular Energetics
- Signal Trafficking (e.g., p11)
- Inflammation
- Network dysregulation

Rubinow DR, Girdier SS. Depress Anxiety. 2011;28(4):282-296.

How Does the Brain Work?

- Signal transmission and processing
- Clusters of neurons into networks: functional outcome
- Networks dynamically assemble
- Synchronization of neuronal firing conveys information
- Distributed neurons provide context

Estradiol Rapidly Induces Synaptic Connections



Srivastava DP, et al. J Neurosci. 2011;31(45):16056-16063.

Our Thinking About Depression has been Misguided

Pathophysiologic confusion



Network Dysfunction in Depression

- Default Mode Network
- Social Cognition Network
- Reward Network
- Affective Regulation Network
- Salience Network

Schiller CE, et al. Compr Physio. 2016;6(3).

E2 Activates the Default Network Estradiol vs. Leuprolide (n = 32)



As compared with ovarian suppression, estradiol replacement increases regional cerebral blood flow (rCBF) in regions of the default network, including the medial prefrontal cortex and precuneus

p = .005, uncorrected; Est = estradiol; Lup = leuprolide; Prog = progesterone

Schmidt PJ, et al. Presented at American College of Neuropsychopharmacology.

Estrous Cycle Regulates the Reward Circuitry

ChR2 female in proestrus



Is this effect modulated by steroid hormones?

Magnitude of operant responding is highest in proestrus

McHenry JA, et al. Nat Neurosci. 2017;20(3):449-458.

Optical self stimulation – 20 Hz ChR2 YFP Control 1500-1500 Active pokes (30 min) *** Active pokes (30') 1000-500-0 600 1200 1800 Ż Ò 0 Time (s)

Our Thinking about Depression has been Misguided

Pathophysiologic confusion

Phenomenologic confusion: Symptoms vs STATE

From Depression to States to Steroids

- Adaptation requires efficient orchestration of networks
- Network output is context and state dependent
- Orchestration through long range connections determines both strength and direction of local connections
- Failure to orchestrate networks results in symptoms (i.e., symptoms are not the locus of pathology)
- Many psychiatric disorders are disorders of state
- State transitions can be manipulated
- Reproductive steroids are informational molecules that "by design" generate behavioral states by acting centrally to integrate a wide array of peripheral actions, perceptions, and behaviors

F. Frohlich Network Neuroscience, Academic Press, 2016.; Sporns O. *Dialogues Clin Neurosci.* 2013;15(3):247-262.; Schiller CE, et al. *Compr Physio.* 2016;6(3).

Gonadal Steroids: A Window into Affective Dysregulation

- •Why think that gonadal steroids have a role in affect regulation?
 - Modulate all pathophysiologic systems implicated in depression
 - Modulate brain regions and networks disturbed in depression
- Do gonadal steroids play a role in reproductive endocrine-related mood disorders?
- If so, why do only some women get these disorders?

E2 Efficacy in Treatment of Perimenopausal Depression



E2 Withdrawal Schematic



E2 Withdrawal Precipitates Depressive Symptoms in Asymptomatic Women with (but not those without) a Past Perimenopausal Depression



Estradiol Decreases Depressive Episodes Over 1 Year in Perimenopausal Women



Estradiol Prevents Depression, Particularly in Those with Recent Stressful Life Events



Gordon BR, et al. JAMA Psych. 2018;75(6):566-576.

Stress and High Variability in Estradiol Interact to Predict Depression in Perimenopausal Women

Steroid Precipitation of PMDD Sxs

Schmidt PJ, et al. N Engl J Med. 1998;338:209-216.

Endocrine Clamp Study

Recurrence of PMDD Symptoms During Initial Exposure to Ovarian Steroids

Mood Symptoms Correlated with Changes in Allo During Progesterone Addback in PMDD Patients

BDI Symptoms Correlated with Changes in Allo During Progesterone Addback in Women with a History of PPD

Figure 3A. There was a trend toward a correlation between the change in Allo levels and emergence of symptoms during Prog addback as measured by PMTS-O in patients but not in controls.

Figure 3B. BDI Scores increased as the levels of Allo decreased in women with a history of PPD but not in controls.

Schiller CE, et al. Psychopharmacology (Berl). 2014;231(17):3557-3567.

Stabilization of Neurosteroid Levels with Dutasteride Prevents the Symptoms of PMDD

Well Women with History of PPD Become Depressed During Scaled-Down Model of the Puerperium

Differential Effects of Steroid Hormones on Mood with HX of PPD

- Hormone sensitivity: 30% increase in negative mood symptoms
- 60% of women with PPD History (hxPPD) were "hormone sensitive"

Schiller C, et al. Presented at American College of Neuropsychopharmacology.

Baseline Reward Anticipation Predicts Hormone Sensitivity

Increased OFC activation is a marker of hormone sensitivity

Schiller C et al. Presented at American College of Neuropsychopharmacology..

Treatments for PND

- Psychotropic Meds:
 - Main consideration is breastfeeding
 - Women may be more sensitive; start at half recommended dose
 - Once effective dose found, treatment x 6-12 months to prevent relapse
- Light therapy
- Omega-3 fatty acids
- Massage
- Vitamin D
- ECT
- Psychotherapy: CBT, IPT, Group, Family/Marital
- Hormonal

Babu GN, et al. Arch Womens Ment Health. 2013;16(3):247-251.; Crowley SK & Youngstedt SD. J Physiol Anthropol. 2012;31(1):15.; Freeman MP, et al. J Affect Disord. 2008;110(1-2):142-148.; Field T, et al. Infant Behav Dev. 2009;32(4):454-60.; Goodman JH & Santangelo G, et al. Arch Womens Ment Health. 2011;14(4):277-293.;Gur EB, et al. Eur J Obstet Gynecol Reprod Biol. 2014;179:110-116.; Gregoire AJ, et al. Lancet. 1996;347(9006):930-933.; Meltzer-Brody S, et al. Nat Rev Dis Primers. 2018;4:18022.; Milgrom J, et al. Aust N Z J Psychiatry. 2015;49(3):236-245.

Efficacy of Estradiol in Postpartum Depression

Gregoire AJ, et al. Lancet. 1996;347(9006):930-933.

Mood Symptoms Correlated with Changes in Allo During Progesterone Addback in PMDD Patients

Figure 3A. There was a trend toward a correlation between the change in Allo levels and emergence of symptoms during Prog addback as measured by PMTS-O in patients but not in controls.

BDI Symptoms Correlated with Changes in Allo During Progesterone Addback in Women with a History of PPD

Figure 3B. BDI Scores increased as the levels of Allo decreased in women with a history of PPD but not in controls.

Schiller CE, et al. Psychopharmacology (Berl). 2014;231(17):3557-3567.

Integrated Hummingbird 202A-C Trial Findings Secondary Endpoints – HAM-D Remission Rates and Response Rates

Integrated Data: HAM-D Individual Items

Anxiety, Psychic

Integrated Data: HAM-D Individual Items

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

Other Concepts, Facts, and Dilemmas in Perinatal Depression

- During pregnancy, there are medications to avoid, but....
 - Who affected: CGMs, mother, newborn, neurobehavioral
 - Who prescribing
 - Dizzying array of conditions
- Inadequacy of database: policy, confounds, interpretation
- There is no free lunch
- Pregnancy affects medication levels
 - Increased volume of distribution, hepatic blood flow
 - Decreased plasma binding proteins
 - Effects of reproductive steroid on metabolic enzymes
- Adherence to and adequacy of treatment (treat the pt, not the blood level)
- Treat all women as if they were pregnant

Bodén R, et al. Arch Gen Psychiatry. 2012;69(7):715-21.; Koren G. J Popul Ther Clin Pharmacol. 2011;18(3):e523-527.

What Causes the Susceptibility?

Lymphoblastoid Cell Line (LCL) Experiments

PMDD: Upregulation of ESC/E(Z) Expression and Differential Response to Estradiol and Progesterone

Dubey N, et al. Mol Psychiatry. 2017;22(8):1172-1184.

CYP7B1 (Oxysterol 7-alpha-hydroxylase) Significantly Upregulated in LCLs from Women with Perimenopausal Depression

Rudzinskas S, et al. Presented at American College of Neuropsychopharmacology.

CXCL10 (Chemokine) Expression is Greater in LCLs in Perimenopausal Depression (PMD) c/c Controls and Particularly During Estradiol Withdrawal

C-X-C Motif Chemokine Ligand 10

- In a cluster among several other CXC chemokines- known biomarker for the development of heart failure and left ventricular dysfunction
- Chemokine elicits its effects by binding to the cell surface chemokine receptor CXCR3
- Activating ERK1/2, p38/MAPK, JNK, and PI3-kinase/AKT signaling pathways, inducing intracellular calcium influx, DNA synthesis, cell proliferation, and chemotaxis
- Works as a chemoattractant for T-cells in inflammatory response

Rudzinskas S, et al. Presented at American College of Neuropsychopharmacology.

SMART Goals Specific, Measurable, Attainable, Relevant, Timely

There are often no right or wrong answers

Remember the 3 Ps

- -Prior history
- -Psychopathology
- -Patient preference

Don't forget to fill out your evaluation on your iPad or online in to collect your credit.

