Impact of Hormonal Changes During Pregnancy and Their Effect on Postpartum Depression:

Can hormonal signals predict who is at risk?

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WOMEN, HORMONES AND STIGMA

97% OF US ALL AGREE... THAT IT'S ALL INTERCONNECTED...

HORMONAL

ACNE...

“I don't want to talk about my hormones.”

“Don't be so emotional.”

“Only those who are qualified...”

“Expert opinion - no evidence required.”

RESPECT MY HORMONES

yes, I am in a bad mood. no, i'm not on my period.
• Reproductive hormones
  estrogen & progesterone

• Play major roles in basic emotion processing, arousal, cognition, & motivation
• Regulate each of the biological systems implicated in major depression
• Have multiple effects on brain function as revealed by brain imaging studies
• Physiologic levels of gonadal steroids modulate the neurocircuitry involved in normal and pathological affective states
• Modulate neural reward function in humans

Estrogen

• Estrogens are the primary female sex hormones and play important roles in both reproductive and non-reproductive systems.
• Estrogens can be synthesized in non-reproductive tissues such as liver, heart, muscle, bone and brain.
• Tissue-specific estrogen synthesis is consistent with a diversity of estrogen actions.

Estrogen synthesis and signaling pathways

Cui et al, 2012

Progesterone to Allopregnanolone Pathway

Oxytocin

The love hormone
  » Lactation
  » Forming social bonds
  » Maternal behaviors
  » Mood
  » Stress
  » Dopamine, Reward
  » Amygdala and Prefrontal Cortex
Normal Lactation Physiology

- **TRH** (+) → **Anterior pituitary** → **Prolactin** → **Milk synthesis** → **Milk ejection reflex**
- **Posterior pituitary** → **Oxytocin** → **Milk secretion**

HPA Stress Axis

- **Stressor** → **Hypothalamus** → **CRH** → **Pituitary** → **ACTH** → **Adrenal** → **Cortisol**
- **Increased vagal tone, maternal behavior**
- **Reduced stress reactivity, decreased depression and anxiety**

Normal Changes in the HPA Axis During Pregnancy and into the Postpartum Period

- **High estrogen and progesterone levels**
- **Rapidly declining estrogen and progesterone**
- **Hyperactive HPA axis with high plasma cortisol**
- **Blunted HPA axis activity due to suppressed hypothalamic CRH secretion**

The Role of Allopregnanolone in PPD

- **ALLO Levels:**
  - **Depression**
  - **Successful ADS Tx**
- **In animal studies, ALLO has been shown to regulate biological processes that are dysregulated in major depressive disorder:**
  - **HPA Axis Regulation**
  - **Neuroprotection**
  - **Immune Function**

Can hormonal signals predict who is at risk?

**YES!**

- There is evidence that reproductive hormones influence the biological systems and neural circuits implicated in depression directly, suggesting that the hormone instability inherent in the perinatal period could contribute to mood dysregulation in PPD.

Risk of Postpartum Psychiatric Episodes and When?

- **Adjusted for age and calendar time.**
- **Psychiatric disorders:** all diagnoses
- **Reference group:** Mothers who gave birth 11 months prior
- **Munk-Olsen et al, JAMA 2006.**
Mean plasma concentrations of estrone (E1), estradiol (E2), estriol (E3), and progesterone (P) during pregnancy. (Data from Tulchinsky D et al 1972; Levitz M et al 1977: 35:109)

The importance of understanding neurobiology

- MRI research can provide information on regional changes in activation in brain regions by detecting regional changes in blood flow.
- But, continued research is needed for both pre- and postpartum anxiety and depression, using a variety of approaches in clinical and preclinical research, to determine the mechanisms behind the neurobiological patterns of activation and deactivation, the physiological correlates of these changes, and the interplay between peripartum mood/emotion and mothering behaviors.
What causes differential sensitivity to changing levels of reproductive hormones during the perinatal period?

Expression of the ESC/E(Z) gene network was found to be systematically disturbed in PMDD.

Applying this novel model to PPD

- New grant support from NIH to apply methodology used in PMDD project:
  - Cellular basis of differential hormone response in peripartum mood disorders (postpartum depression and postpartum psychosis)
- Partnership with Crystal Schiller and David Rubinow at UNC, and Peter Schmidt and David Goldman at NIH and Veerle Bergink from Erasmus in the Netherlands.
- This new study will examine women with hormone susceptible phenotypes of PPD and PPP to
  1) to create human-induced pluripotent cells (h-iPCs) and neuronal progenitor cells whose transcriptional responses to ovarian steroids in vitro will be assessed;
  2) to create lymphoblastoid cell lines (LCLs).

The PACT Consortium—Postpartum Depression: Action Towards Causes and Treatment

- Impetus for the PACT Consortium
  - Strong belief in common goal
  - Identifying biomarkers of susceptibility/risk is achieved by large-scale collaborative effort
- Long-term goal
  - International consortium focused on elucidating the causes of postpartum psychiatric illness

Creation of PACT

- Collaborative spirit! Formed in 10/10 at Marce meeting in Pittsburgh
- Modeled on principles of the highly successful Psychiatric Genomics Consortium (PGC)
- Democratic and inclusive consortium open to all who agree to operating principles
- All effort is donated, and there are no entry fees

PACT: Members and Process

- PACT: Members are from well over 20 institutions in 9 countries. Comprehensive phenotypic data on ~18,000 unique subject records of women with PPD was submitted by 120 PACT sites.
- PACT MOU details intellectual property, authorship, and rules of conduct
- PACT committees include the executive/coordinating and phenotype groups
Definition and Phenotypic Heterogeneity

- Epidemiology: PPD is common & devastating
- Definition: Episode of MDD occurring postpartum
- Distinguishing characteristics: Severe anxiety, agitation, & suicidal thoughts
- Timing of symptom onset—Do symptoms begin before or after childbirth? Does it matter?
- Prior Psychiatric Comorbidity: Anxiety and MDD
- Pregnancy and Obstetrical Complications: May play a role in determining PPD onset

Understanding the genetic basis of perinatal depression informed by work in other Psychiatric conditions

- Work on major depressive disorder demonstrated need for large sample size
  - In a large Swedish study, postpartum depression (PPD) shown to be heritable subtype of MDD

PPD ACT

- Novel iPhone Study to Investigate Genetic Risks of Postpartum Depression
In partnership with Apple, UNC launched novel PPD study that is highly scalable and low-cost

**Launch Date:** March 21, 2016

**Purpose:** To understand why some women suffer from PPD and others do not. Ultimately with the aim of improving detection, prevention and treatment.

**Study Description:**
- Survey delivered via app to identify women who have had symptoms of PPD
- Eligible women invited to provide DNA samples

**Highlights:**
- Informed consent built into the app
- US and Australia (Canada and UK soon)
- UNC IRB approved (US version)

PPD ACT possible because of partnerships—this is team science!

UNC Center for Women’s Mood Disorders
UNC Genetics and Psychiatry Collaboration
UNC NIC and SOM Center for Innovation

Launch supported by marketing campaign including web, social media, media interviews


After one month 10,000 women enrolled and 5,000 donating DNA

Goal to reach 50,000 women worldwide

Notably severe cohort of women providing DNA is good for genetic analysis

While not a specific objective of the study, many women sought treatment with a local mental health provider after using the mobile app
What’s next for PPD ACT
• US and Canada expanding to Android version in the next few months
• New international sites – Canada, UK, Denmark
• Addition of new modules to understand economic impact
• Ongoing support from Postpartum Progress
• New support from Sage Therapeutics

Conclusions
• This is an incredibly exciting time for research in women’s reproductive mood disorders.
• Novel scientific approaches will allow us to elucidate the underlying causes of postpartum mood disorders leading to efforts to identify those at risk and improve treatment.
• Hormonal signals will play an important role in predicting who is at risk.

UNC Perinatal Psychiatry Inpatient Unit
• 1st freestanding Perinatal Inpatient unit in the US – renovated summer 2011
• Provides specialized, comprehensive assessment and treatment
  – Medication stabilization
  – Individual and group counseling and behavioral therapy
  – Partner assisted therapy, family therapy, maternal-infant interaction, & Psychoeducation for both patients and spouses
  – Biofeedback, spirituality, yoga, consultations from lactation specialists & registered dieticians

UNC PPIU
• Comfort measures
  – Home-like atmosphere
  – Protected sleep times
  – Gliders and supplies for pumping/feeding
  – Pumps, supplies and refrigerator for milk storage
  – Specialty perinatal nursing staff (dual Psych and OB training)
    • 3-5 patients per 1 RN
  – State-of-the-art treatment
  – Extending visiting hours to maximize positive mother-baby interaction
  – Provides an outstanding place to conduct novel RESEARCH PROTOCOLS
• Sage-547 allopregnanolone study for severe postpartum depression
UNC Center for Women’s Mood Disorders: Perinatal Psychiatry Program

Clinical and Research Program that provides assessment, treatment and support for women in the perinatal period

Collaboration of doctors, nurses, midwives, therapists, & social workers

www.womensmooddisorders.org

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