Harnessing the Power of Social Media:

Investigating the Genetics of Post-Partum Depression using the Apple ResearchKit

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UNC Center for Women’s Mood Disorders
Disclosures

• NIH R01MH104468, R01MH095992, R01 HD073220-01
• NC TraCS
• J&J/Jansen
• Foundation of Hope
• Sanders Clinician Scholar
• Sage Therapeutics
Postpartum depression: a disorder in search of a definition

Katherine L. Wisner · Eydie L. Moses-Kolko · Dorothy K. Y. Sit
Perinatal depression is common, morbid & often missed

- **Common**
  - **10-15% prevalence**
  - Most common, unrecognized perinatal complication

- **Morbid**
  - Low maternal weight gain
  - Preterm birth
  - Impaired attachment
  - Increased suicide and infanticide

- **Missed**
  - Inconsistent use of practice guidelines and routine screening
  - Symptoms can differ from “classic depression”

By KJ DELL'ANTONIA JUNE 16, 2014 NYT
Distinguishing Characteristics of Perinatal Mood Symptoms

- Anxiety or agitation
- Depressed Mood
- Sadness, weepiness
- Irritability
- Hypervigilance about the baby
- OR Lack of interest in the newborn
- Impaired concentration or feeling overwhelmed
- Feelings of dependency or guilt
Postpartum Psychosis

- A rare condition, with an estimated prevalence of 0.1%-0.2% (one to two per thousand)
  However, in women with Bipolar Disorder, the risk is 100 times higher at 10% - 20%
  It is a psychiatric emergency & requires immediate treatment with a mood stabilizer & antipsychotic
- Onset usually 2-3 days postpartum
- Has a 5% suicide & 4% infanticide rate
- Risk for recurrent episode with a subsequent pregnancy is high

Suicide is the second leading cause of death in postpartum women
Barriers to Diagnosis & Treatment

Study Links Autism With Antidepressant Use During Pregnancy

If you were prescribed Zoloft® while you were pregnant and gave birth to a baby with a congenital heart defect, persistent pulmonary hypertension of the newborn (PPHN), an abdominal defect, a
Consequences of Untreated Antenatal Depression

- Consistently associated with preterm birth
- Decreased breastfeeding initiation
- Increased risk of postpartum depression
- Fetal effects—hyperactivity, irregular fetal heart rate
- Newborn effects—increased cortisol and norepinephrine levels, decreased dopamine levels, altered EEG patterns, reduced vagal tone, stress/depressive-like behaviors, and increased rates of premature deaths and neonatal intensive care unit admission

- Grigoriadis S, 2013, J Clin Psych
- Gaillard A, 2014, Psychiatry Research
- Roomruangwong C, 2016 Psychiatry Research
- Gentile S, 2015 Neuroscience
Original Investigation  JAMA Psychiatry 2013

Maternal Depression During Pregnancy and the Postnatal Period
Risks and Possible Mechanisms for Offspring Depression at Age 18 Years

Rebecca M. Pearson, PhD; Jonathan Evans, MD; Daphne Kounali, PhD; Glyn Lewis, PhD; Jon Heron, PhD;
Paul G. Ramchandani, DPhil; Tom G. O’Connor, PhD; Alan Stein, FRCPsych
Results

• Antenatal depression independent risk factor. Offspring were 1.28 times (95%CI, 1.08-1.51; P = .003) more likely to have depression at age 18 yrs for each s.d. increase in antenatal maternal depression score independent of later maternal dep

• PPD was also risk factor for mothers with low educ. Offspring 1.26 times (95%CI, 1.06-1.50; P = .01) more likely to have depression for each s.d. increase in PPD score.
Continuum of Care of Perinatal Behavioral Health Services

Outpatient Clinic Services
(≈95% of all women served)

UNC Center for Women’s Mood Disorders provides ≈3,000 outpatient visits per year

Inpatient Treatment
(most severely ill 5%)

UNC Perinatal Psychiatry Inpatient Unit has up to 5 beds depending on census

Community Treatment
(education and support services)
Risk of Postpartum Psychiatric Episodes and When?

Adjusted for age and calendar time. Psychiatric disorders: all diagnosis

Reference group: Mothers who gave birth 11 months prior.

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.)
Precipitous Drop in Hormones at Birth

[Diagram showing changes in hormone levels over days from parturition, with peaks for progesterone, relaxin, fetal cortisol, estrogens, PGF$_{2a}$, oxytocin, maternal cortisol, and prolactin.]
PACT--Postpartum Depression: Action Towards Causes and Treatment

• Impetus for PACT
  • strong belief in common goal
  • identifying biomarkers of susceptibility is achieved by a 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 28 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
## PACT Supplement Table 1

Study Site Locations, Collaborators, Design and Records Submitted

<table>
<thead>
<tr>
<th>Country</th>
<th>Institution</th>
<th>Collaborators</th>
<th>Study Designs Submitted</th>
<th>Records Submitted</th>
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<tbody>
<tr>
<td>Australia</td>
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<td>Buist, A., Biluta, I. *</td>
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<td>Denmark</td>
<td>Aarhus University</td>
<td>Munk-Olsen, T. Epidemiologist</td>
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</tbody>
</table>

* Data submitted included study participants across multiple cohorts
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
Edinburgh Postnatal Depression Scale (EPDS)

- 10-item self-report questionnaire that assesses depressive and anxious symptoms

- The most widely used and validated screening tool for in pregnant and postpartum women
  - Cut off score ≥12 indicates MDD
  - Cut-off ≥10 indicates minor depression that require additional clinical monitoring
## 10 Item Edinburgh Postnatal Depression Scale

<table>
<thead>
<tr>
<th>Item</th>
<th>Question</th>
<th>Often</th>
<th>Sometimes</th>
<th>Hardly Ever</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>During the worst episode... How often did you feel able to laugh or see the funny side of things?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>How often were you able to look forward to things with excitement?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>How often did you blame yourself unnecessarily when things went wrong?</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>How often were you anxious or worried for no good reason?</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>How often did you feel scared or panicky for no good reason?</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>How often did you feel overwhelmed?</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>How often were you so unhappy that you had difficulty sleeping?</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>How often did you feel sad or miserable?</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>How often were you so unhappy that you cried?</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>How often did the thought of harming yourself occur to you?</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
Latent Class Analysis (LCA)

• The central premise of LCA is that a heterogeneous group can be reduced to several homogeneous subgroups through evaluating and then minimizing associations among responses across multiple indicator variables.

• LCA techniques cluster similar response profiles for distinct class membership among cases.
Identifying PPD phenotypic heterogeneity
A two-tier analysis approach

PACT Unique Subjects
N= 17912

Tier 1 LCA
Subjects with complete EPDS Item Data
N=6556

Tier 2 LCA
PPD Case Definition Subjects with Depression Rating Score
N=4245

Subjects Included in Both Tier Analyses
N=2527*

* Subjects were excluded due to incomplete data and/or not fulfilling the PPD Case Definition
Heterogeneity of postpartum depression: a latent class analysis

Postpartum Depression: Action Towards Causes and Treatment (PACT) Consortium

Summary
Background Maternal depression in the postpartum period confers substantial morbidity and mortality, but the definition of postpartum depression remains controversial. We investigated the heterogeneity of symptoms with the aim of identifying clinical subtypes of postpartum depression.

Methods Data were aggregated from the international perinatal psychiatry consortium Postpartum Depression: Action Towards Causes and Treatment, which represents 19 institutions in seven countries. 17,912 unique subject records with phenotypic data were submitted. We applied latent class analyses in a two-tiered approach to assess the validity of empirically defined subtypes of postpartum depression. Tier one assessed heterogeneity in women with complete data on the Edinburgh postnatal depression scale (EPDS) and tier two in those with postpartum depression case status.
Heritability of PPD

Genetic influences on post-natal depressive symptoms: findings from an Australian twin sample

S. A. TRELOAR, N. G. MARTIN, K. K. BUCHOLZ, P. A. F. MADDEN and A. C. HEATH

From the Queensland Institute of Medical Research, Brisbane, Queensland, Australia; and Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA

Retrospective interview and questionnaire data from 838 parous female twin pairs (539 monozygotic, 299 dizygotic)

Genetic factors explained 38% of variance in PNDS (95% confidence interval 26–49%)
The Swedish Twin Registry

- The Swedish Twin Registry at Karolinska Institutet

- Collaboration with Dr. Paul Lichtenstein, Dr. Patrik Magnusson, and Dr. Alexander Viktorin

- Our work together began in 2008, when lifetime EPDS was added to SALTY interview.
Estimating Heritability

\[ A + C + E = 1.0 \]

\[ A^2 = \text{heritability (genomics)} \]

\[ C^2 = \text{environmental effect shared between members of twins (ie: parenting, water)} \]

\[ E^2 = \text{environment specific to each individual person (infection versus abuse)} \]
Tetrachoric Correlation

• Tetrachoric correlation: correlation coefficient describing the relationship between discrete variables and is used in twin modeling

• Because MZ is greater than DZ it is consistent with a genetic effect

<table>
<thead>
<tr>
<th>Tetrachoric correlation</th>
<th>MZ</th>
<th>95% CI (0.287-0.695)</th>
<th>DZ</th>
<th>95% CI (-0.206-0.404)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R=0.491</td>
<td>SE=0.104</td>
<td></td>
<td>R=0.0988</td>
<td>SE=0.1557</td>
</tr>
</tbody>
</table>
Heritability of PPD in STR

• 2321 parous twins in the Swedish twin study using the classical twin-model followed with an extended multivariate sibling design including over 1 million parous female siblings.

• Heritability of PPD was estimated at 54% (95% CI, 35-70%) and demonstrated that the heritability of PPD is higher than that for MDD.

• Alexander Viktorin, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
Objective: The authors investigated the relative importance of genetic and environmental influences on perinatal depression, and the genetic overlap between perinatal depression and nonperinatal depression.

Method: Analyses were conducted using structural equation modeling for 1) the lifetime version of the Edinburgh Postnatal Depression Scale in 3,427 Swedish female twins and 2) clinical diagnoses of depression separated into perinatal depression and nonperinatal depression in a Swedish population-based cohort of 580,006 sisters.

Results: In the twin study, the heritability of perinatal depression was estimated at 54% (95% CI=35% – 70%), with the remaining variance attributable to nonshared environment (46%; 95% CI=31% – 65%). In the sibling design, the heritability of perinatal depression was estimated at 44% (95% CI=35% – 52%) and the heritability of nonperinatal depression at 32% (95% CI=24% – 41%). Bivariate analysis showed that 14% of the total variance (or 33% of the genetic variance) in perinatal depression was unique for perinatal depression.

Conclusions: The heritability of perinatal depression was estimated at 54% and 44%, respectively, in separate samples, and the heritability of nonperinatal depression at 32%. One-third of the genetic contribution was unique to perinatal depression and not shared with nonperinatal depression, suggesting only partially overlapping genetic etiologies for perinatal depression and nonperinatal depression. The authors suggest that perinatal depression constitutes a subset of depression that could be prioritized for genomic discovery efforts. The study findings have direct translational impact that can assist clinicians in the counseling of their patients regarding risk and prognosis of perinatal depression.

AJP in Advance (doi: 10.1176/appi.ajp.2015.15010085)
Maternal Depression Often Starts Before Giving Birth, Study Says

By PAM BELLUCK  FEBRUARY 2, 2015 6:05 PM  22 Comments

A large new study has documented unexpected links in the timing and severity of symptoms of maternal depression, which could help mothers and doctors better anticipate and treat the condition.
Understanding the genetic basis of perinatal depression informed by work in other Psychiatric conditions

UNC Psychiatric Genomics Consortium (PGC)
- >800 investigators from 38 countries
- Genetic samples from >900,000 individuals
- Meta- and mega-analyses of genome-wide genomic data
- Psychiatric disorders

• 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

Difficult and expensive to achieve large sample size with traditional research methods
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!
Launch supported by marketing campaign including web, social media, media interviews
Generated incredible media response: New York Times, CNN, Business Wire, Huffington Post,
After one month 10,000 women enrolled and 5,000 donating DNA

**Daily Enrollment**

- Days after launch

**Age of Participants**

- Median age = 33

Goal to reach 50,000 women worldwide
Notably severe cohort of women providing DNA is good for genetic analysis.

EPDS Scores for Cases (Score ≥13)

![Histogram](image)

Median Score = 23

While not a specific objective of the study, many women sought treatment with a local mental health provider after using the mobile app.
Welcome to PPD ACT

Postpartum Depression: Action towards Causes and Treatment

A Genetic Research Study of Postpartum Depression

Join Study
Following the birth of your 3rd child, did feeling sad, miserable, or very anxious interfere with your day-to-day life?

- Often *
- Sometimes
- Rarely
- Never
Data Collection

This study is about postpartum depression and we are collecting data about women's experiences following childbirth. Some women may be asked to take part in a genetic part of the study.
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
Thanks!

- PACT Consortium

- UNC Center for Women’s Mood Disorders
  - PPD ACT Team
    - Patrick Sullivan, MD
    - Jerry Guintivano, PhD
    - Carol Lewis, MBA
    - Holly Krohn, MPH

www.womensmooddisorders.org
LEFT TO RIGHT: Patrick Sullivan, Jerry Quintivano, Samantha Meltzer-Brody, Carol Lewis, Holly Krohn at University of North Carolina at Chapel Hill