Does Fetal Exposure to Maternal Stress Influence Child Development?

Poverty and the Long Term Effects of Early Life Experience
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The Earliest Origins of Health
Poverty and Child Health Problems

- Any limiting chronic condition
- Asthma prevalence
- Ear disease
- Injury
- Physical inactivity

Percentage

SES (lowest to highest)

Poverty and Child Cognitive Development

The graph illustrates the relationship between the age of a child and their score percentile across different income quartiles. The highest income quartile shows a steady increase in score percentile as the child grows older, whereas the lowest income quartile shows a decline. The second and third income quartiles fall in between, with the third quartile showing a slight increase and the second quartile maintaining a relatively stable score percentile.
WHO ARE THE POOREST AMERICANS TODAY?

Poverty by Age Group

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Percent in Poverty</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5</td>
<td>26%</td>
</tr>
<tr>
<td>6-17</td>
<td>20%</td>
</tr>
<tr>
<td>18-24</td>
<td>18%</td>
</tr>
<tr>
<td>25-34</td>
<td>13%</td>
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<tr>
<td>35-44</td>
<td>11%</td>
</tr>
<tr>
<td>45-54</td>
<td>8%</td>
</tr>
<tr>
<td>55-59</td>
<td>10%</td>
</tr>
<tr>
<td>60-64</td>
<td>11%</td>
</tr>
<tr>
<td>65-74</td>
<td>10%</td>
</tr>
<tr>
<td>75+</td>
<td>14%</td>
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</tbody>
</table>
Poverty and Birth Outcome

Poverty is associated with a 1.5 to 2.5 fold increase in risk of low birth weight (< 2500 grams)

Nkansah-Amankra et al.; 2010, Stein et al., 1987; O'Campo et al., 1997
SES and Low Birth Weight

Reichman, 2005
Birth Phenotype Predicts Disease in Adulthood

- Coronary artery disease
- Hypertension
- Diabetes
- Impaired pulmonary function/Asthma
- Endocrine cancers
- Osteoporosis
- Obesity
Birth Phenotype Predicts Child and Adult Psychopathology

- Autism
- ADHD
- Affective disorders/Suicide
- Schizophrenia
Is there a direct association between measures of the prenatal environment and child and adult health and development that is independent of birth phenotype?
Do the prenatal and early postnatal environments interact to shape lifespan development?
GENERAL AIM:
Determine the influence of the prenatal and early postnatal periods on development of the human fetus, infant, child and……

THE FINDINGS REPORTED HERE:

- INCLUDE HEALTHY ADULT WOMEN
- INCLUDE HEALTHY CHILDREN
- INCLUDE ONLY CHILDREN BORN FULL TERM
- CONSIDER RELEVANT COVARIATES INCLUDING POSTNATAL MATERNAL STRESS AND SOCIODEMOGRAPHIC FACTORS
MODEL FOR PROSPECTIVE STUDIES

- Fetal exposure to stress over course of gestation
- Neonatal functioning
- Infant and child neurodevelopmental trajectories
  - Emotional development
  - Cognitive & motor development
  - Brain development

- Fetal maturation
- Birth outcome

GENETIC AND EPIGENETIC CONTEXT
Hypothalamic Pituitary Adrenal Axis (HPA Axis)
The regulation of the HPA and placental axis changes dramatically over the course of HUMAN gestation with profound implications for the mother and the fetus.
Endocrine Changes During Pregnancy

**CRH**
- x 40

**ACTH**
- x 3

**Salivary Cortisol**
- x 2

**Plasma Cortisol**
- x 2.5

**Estradiol**
- x 5

**Progesterone**
- x 4
WHAT ABOUT BIRTH PHENOTYPE AND STRESS?

RATE OF CHANGE OF PLACENTAL CRH IS ASSOCIATED WITH PRETERM DELIVERY

Preterm vs. Term (includes week 36) CRH
All subjects
N=436

CRH (pg/ml)

Weeks Gestation

0 100 200 300 400 500 600

preterm

term
CRH and Tadpole Metamorphosis

Denver (in Smith, 1999)
How does prenatal exposure to psychobiological stress signals influence development?

**Two Approaches**

- Natural variations in maternal psychological and biological stress signals during pregnancy
- Administration of synthetic stress hormones (glucocorticoids) during pregnancy
Assessment Protocol

12-36+ GA  |  Birth  |  24 hrs  |  3-24 months  |  5-8 yrs old
These influences on the fetus have been described as “programming.” The human fetus expresses eight times more cell divisions before term compared with cell divisions during the remainder of life (Barker, 1998).

Susceptible to both organizing and disorganizing influences which can alter the fetal developmental trajectory with lasting influences on health.
Brain Development

By seven weeks nerve cells in brain have begun touching and forming primitive nerve paths

Over 100,000 nerve cells/minute

At birth the baby will have 100 billion cells

Towards the end of gestation synapses are forming at a rate of 40,000 per second.

Proliferation, migration differentiation, synaptogenesis, myelination.
NEONATAL MATURITY: THE BALLARD

Cortisol and placental CRH → Maturity

The effects were stronger in males

Developmental Psychobiology, 2008, 50, 232-241
Stress Responses: Heel-stick Blood Draw
Prenatal Maternal Cortisol and Infant Stress Regulation

Davis et al., 2011 *Child Psychology and Psychiatry*
Prenatal Maternal Cortisol and Infant Stress Regulation

Davis et al., 2011 Child Psychology and Psychiatry
EXPOSURE TO ELEVATED MATERNAL CORTISOL PREDICTS INFANT HPA REGULATION AT 2, 6 AND 12 MONTHS

INFANT CORTISOL RESPONSE TO INNOCULATION

INFANT CORTISOL RESPONSE IS RELATED TO PRENATAL EXPOSURE
Laboratory Temperament Assessment
Laboratory Temperament Assessment

- Challenge Room
- Male Stranger
- Female Stranger
- Puppet Show
Prenatal Maternal Cortisol and Toddler Fear/Anxiety

Fear Score

- Challenge Task
- M Stranger
- Puppet Show
- F Stranger

Low Prenatal Cortisol
High Prenatal Cortisol

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Prenatal Maternal Cortisol and Childhood Anxiety at 5 years

Sample Anxiety Items

Iggy: “I don't have lots of bad dreams.”

Ziggy: “I do have lots of bad dreams.”

Iggy: “I get nervous when my teacher asks me a question.”

Ziggy: “I don’t get nervous when my teacher asks me a question.”

N=41
Prenatal Maternal Cortisol and Child Behavior Problems at 6 to 8 years

Anxious/Depressed

- Low Prenatal Cortisol
- High Prenatal Cortisol

Maternal Report
Sample Items
- Clings to adults.
- Fears going to school.
- Nervous, high-strung, or tense

N=181

Davis & Sandman, 2012 Psychoneuroendocrinology
Stress and the Amygdala

Mitra et al., 2005

Ono et al., 2008
Fetal exposure to maternal cortisol is associated with child brain development

Higher maternal cortisol concentrations in early gestation are associated with larger right amygdala volume and affective problems (CBCL) in girls at 6-9 years age.

The magnitude of the effect is substantial; a 1 standard deviation increase in maternal cortisol is associated with an a 6.4% increase in the size of the right amygdala.

Buss et al., Proceedings of the National Academy of Science, 2012, 109, E1312-1319
Fetal exposure to synthetic glucocorticoids is associated with cortical thinning during childhood.

Davis et al., in press *Biological Psychiatry*
Conclusions

• The fetal period in the life cycle is unmatched in growth and development.

• It is the period in the human life span that is most vulnerable to both organizing and disorganizing influences.

• Despite these facts, the developmental consequences of fetal exposures are understudied and poorly understood.

• Our data support the possibility that gestational exposure to stress hormones increases stress reactivity and vulnerability to anxiety problems.
Is there a viability vulnerability trade off? Sex differences in fetal programming.

Sexually specific patterns are formed very early in development.

Males are more vulnerable to threats to viability.

Are females more vulnerable to more subtle outcomes that may not be apparent until later in life? Is this especially true for mental health problems?

Sex specific responses of the fetus and the placenta to stress may contribute to these differences.
Preconception Stress

Rodents

• Adult offspring memory functioning (Schelar et al., 2007)
• Affective and social behaviour (Shachar-Dadon et al., 2009)
• Long term impairments in brain functioning and plasticity (Huang et al., 2010)
Preconception Stress

**Human**

- **Stillbirth** (Witt, et al., 2011; Wisborg et al., 2008)
- **Adverse birth outcome** (Class et al., 2011; Witt, et al., 2011)
- **Infant mortality** (Class et al., in press)

- **Childhood ADHD** (Li et al., 2010)
- **Adult affective disorder** (Khashan et al., 2011)
- **Schizophrenia and Bipolar Disorders** (Class et al, in press)
Pre-Pregnancy Maternal BMI and Child ADHD symptoms

Buss et al, 2012 PLoS ONE
Pre-Pregnancy Maternal Exposure to Stressful Life Events and Child Attention Problems

![Bar chart showing Attention Problems T-Score by Life Events]
Pre-Pregnancy Maternal Exposure to Stressful Life Events
Model of **chronic** early-life Stress in rodents

- Limited nesting material for one week, (P2-P9*),
- This leads to chronic stress in the pups, as measured by biochemical markers. Stress dissipates rapidly but:
- In adolescence: vulnerability to depression, cognitive problems
- Major disruption of hippocampal neuron structure and function

Brunson, J Neurosci 2 005; Ivy. Neurosci, 2008; J Neurosci, 2010
To understand early life influences on development it is critical to evaluate the way that the prenatal environment “prepares” the fetus for the postnatal world.
CONCLUSIONS

“INVEST IN INFANT STRUCTURE”

Paraphrase of President Barak Obama
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