Interaction of prenatal psychosocial stress and nutrition: implications for maternal and infant metabolic outcomes

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Introduction

DOHaD theory – exposures/insults occurring at sensitive periods of gestation may adversely impact fetal development with long-term implications for health and disease outcomes

Nutrition

Azad et al., 2016; Horan et al., 2014, 2016; Donahue et al., 2011; Drake & Reynolds, 2010; Moon et al., 2013; Okubo et al., 2014; Reynolds et al., 2011

Stress

Brunton et al., 2013; Dancause et al., 2015; Entringer et al., 2008, 2010; Gillman et al., 2006; Jasarevic et al., 2015; Mueller et al., 2006; Tamashiro et al., 2009;

Offspring obesity risk / metabolic dysfunction

Azad et al., 2016; Horan et al., 2014, 2016; Donahue et al., 2011; Drake & Reynolds, 2010; Moon et al., 2013; Okubo et al., 2014; Reynolds et al., 2011
Introduction

Combined effects of nutrition and stress on fetal programming are poorly studied.
Bi-directional relationship between nutrition & stress

Stress influences nutrition:
- Quantity & quality of food consumed
- Metabolic response to ingested food
- Metabolic fate in target tissues

Nutrition influences stress:
- Perception of stress, mood
- Glucocorticoid response
- Inflammatory response

T.C. Adam, E.S. Epel / Physiology & Behavior 91 (2007) 449–458
Mediating role of inflammation

"Westernized diet"
• Refined starches
• Sugars
• Trans fat
• High n-6/n-3 ratio
• Processed meats

"Health conscious diet"
• Vegetables
• Fruits
• Fish
• Olive oil
• Wholegrains

Inflammation

Depression

Giugliano et al., 2006; Lopez-Garcia et al., 2004, 2005; Mozaffarian et al., 2009

Kiecolt-Glaser et al., 2010

Howren et al., 2009; Miller et al., 2006; Raison et al., 2006

Esposito et al., 2002, 2003; Estruch, 2010; Bogani et al., 2007
# Evidence for prenatal nutrition x stress interactions

<table>
<thead>
<tr>
<th>Ref &amp; study design</th>
<th>Population</th>
<th>Diet assessment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hurley et al., 2005; prospective observational</td>
<td>134 low-risk pregnant women, USA</td>
<td>FFQ at 28 weeks</td>
<td>Stress &amp; anxiety associated with ↑ intake of breads, fats, oils, snacks, total energy, Fe, Zn</td>
</tr>
<tr>
<td>Golding et al., 2009; Santos-Vaz et al., 2013; retrospective cross-sectional</td>
<td>&gt;9000 women ALSPAC cohort, UK</td>
<td>FFQ at 32 weeks to assess n-3 intake from seafood and dietary patterns</td>
<td>Low or no n-3 intake ↑ risk of depressive symptoms &amp; anxiety; health conscious &amp; traditional diet patterns ↓ risk anxiety</td>
</tr>
<tr>
<td>Chatzi et al., 2011; Retrospective observational</td>
<td>529 healthy pregnant women, Greece</td>
<td>FFQ mid-pregnancy, dietary pattern analysis</td>
<td>Olive oil &gt;40g/day ↓ risk postpartum depression; sugar &gt;29g/day ↑ risk</td>
</tr>
<tr>
<td>Vilela et al., 2014; Prospective observational</td>
<td>207 healthy pregnant women, Brazil</td>
<td>FFQ in trimester 1 to assess preconception diet</td>
<td>Healthy and traditional diet patterns --vely associated with anxiety from prenatal to postpartum period</td>
</tr>
<tr>
<td>Chang et al., 2015; cross-sectional qualitative</td>
<td>96 low-income overweight &amp; obese women, USA</td>
<td>Focus groups to explore health knowledge &amp; attitudes towards healthy eating and exercise</td>
<td>Barriers to healthy eating: poor self-control, lack of social support, financial constraints. Facilitators: behavioral capacity, autonomous motivation (e.g. concerns re GDM)</td>
</tr>
</tbody>
</table>
Evidence for prenatal stress effects on offspring metabolic states

Experimental animal studies:
• ↑ body weight/postnatal growth (Amugongo et al., 2014; Mueller et al., 2006)
• ↓ glucose tolerance/insulin sensitivity (Balasubramian et al., 2015; Lasage et al., 2004)
• Dyslipidemia (Brunton et al., 2013)

Animal study of prenatal stress +/- high fat diet:
• ↑ leptin and impaired glucose tolerance (Tamashiro et al., 2009)

Observational human studies:
• ↓ birthweight – combined maternal depression & anxiety (Loomans et al., 2012)
• ↑ adiposity & BMI at age 2.5y (Dancause et al., 2015)
• ↑ BMI, insulin insensitivity & VLDL in early adulthood (Entringer et al., 2008)
Conceptual Framework: Fetal programming by prenatal nutrition & stress

Prenatal exposures

- Psychological stress, anxiety, social support
- Behavioral diet, physical activity, sleep, substance abuse
- Biophysical prepregnancy BMI, gestational weight gain

MATERNAL COMPARTMENT IN PREGNANCY
- Endocrine
- Inflammatory
- Nutrition
- Glycemic

GESTATIONAL BIOLOGY

FETAL COMPARTMENT

Newborn Adiposity/metabolic function
Offspring health outcomes
Postnatal exposures

Postnatal exposures
Characterization of prenatal nutrition & stress

**Prenatal Nutrition**
- Dietary intake – quantity & quality
- Biophysical status – BMI, fat mass, lean mass
- Nutritional metabolites – fatty acids, amino acids etc. available to the fetus

**Prenatal Stress**
- Psychosocial – stress, anxiety, social support, depression
- Corticotrophin releasing hormone (CRH)
- Glucocorticoids - cortisol
- Inflammatory cytokines
Overview of EMA Study
Ecological Momentary Assessment (EMA) study at UCI
(N=250 mothers)

- Baseline Blood/ Hair Sample
- Fasting Blood Sample
- Psychosocial Stress Assessment
- Neuropsychological Battery
- Fetal Ultrasound
- Cervicovaginal Swabs
- Anthropometric Measures
- 4 Day Ambulatory Period:
  - Diurnal Salivary Cortisol (7 per day)
  - Actiheart Device (beat to beat heart rate)
  - Electronic Diary (Smart Phone)
  - 3 x 24-hr Dietary Recall Assessments
  - 24 hr Urine

- Delivery: Placenta, cord
  blood and cord tissue
  (telomere biology)
  2-4 weeks
- Newborn Body
- Infant Body
  Composition (DXA)
- Total Energy
  Expenditure
- Blood, Saliva, Hair
- Infant Environment
  (HOME)
- Infant Cognitive, Motor
  & Emotional Behavior
  (Bayley’s)
- Infant Motor
  Performance (TIMP)
- Infant Body
  Composition (DXA)
- Total Energy
  Expenditure
- Anthropometrics
- Blood, Saliva, Hair
  Samples
- Infant MRI (brain:
  structural MRI, DTI,
  resting state fMRI; body:
  whole body scans,
  brown fat scans)
- Infant Cognitive, Motor
  & Emotional Behavior
  (Bayley’s)
- Mother/Infant
  Attachment (Strange
  Situation)

Pre-pregnancy BMI
“real time” assessment of maternal psychosocial states
Nutrient & food group intakes
Overall diet quality
EMA Study: Assessing diet & psychosocial states

Alternative Healthy Eating Index adapted for Pregnancy (AHEI-P)
- Validated index of diet quality in prenatal populations (Rifas-Shiman et al., 2009; Rodriguez-Bernal et al., 2010)
- 10 components:
  - Vegetables
  - Fruit
  - cereal fiber
  - vegetable protein
  - white/red meat
  - PUFA/SFA
  - trans fat
  - folate
  - iron
  - calcium

Ecological Momentary Assessment (EMA) of psychosocial states
- Immediate reports of current state or activity
- Collected in naturalistic settings
- Maternal perceived stress, positive/negative mood, social support
- Multiple times/day over 4 days in each trimester
## Association of diet quality with maternal psychosocial states

### Trimester 1 AHEI-P

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>B</th>
<th>95% CI</th>
<th>P unadjusted</th>
<th>P adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perceived stress</td>
<td>207</td>
<td>-0.010</td>
<td>-0.017 -0.003</td>
<td>0.007</td>
<td>0.003</td>
</tr>
<tr>
<td>Positive mood</td>
<td>207</td>
<td>0.012</td>
<td>0.003 -0.020</td>
<td>0.006</td>
<td>0.004</td>
</tr>
<tr>
<td>Negative mood</td>
<td>207</td>
<td>0.000</td>
<td>-0.004 -0.005</td>
<td>0.922</td>
<td>0.907</td>
</tr>
<tr>
<td>Social support</td>
<td>202</td>
<td>0.009</td>
<td>0.001 -0.018</td>
<td>0.034</td>
<td>0.030</td>
</tr>
</tbody>
</table>

* Adjusted for maternal pre-pregnancy BMI and age

### Trimester 2 AHEI-P

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>B</th>
<th>95% CI</th>
<th>P unadjusted</th>
<th>P adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perceived stress</td>
<td>210</td>
<td>-0.006</td>
<td>-0.014 -0.001</td>
<td>0.110</td>
<td>0.048</td>
</tr>
<tr>
<td>Positive mood</td>
<td>210</td>
<td>0.007</td>
<td>-0.002 -0.016</td>
<td>0.141</td>
<td>0.083</td>
</tr>
<tr>
<td>Negative mood</td>
<td>210</td>
<td>-0.004</td>
<td>-0.009 -0.002</td>
<td>0.192</td>
<td>0.101</td>
</tr>
<tr>
<td>Social support</td>
<td>206</td>
<td>0.003</td>
<td>-0.006 -0.013</td>
<td>0.483</td>
<td>0.455</td>
</tr>
</tbody>
</table>

### Trimester 3 AHEI-P

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>B</th>
<th>95% CI</th>
<th>P unadjusted</th>
<th>P adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perceived stress</td>
<td>204</td>
<td>-0.008</td>
<td>-0.016 -0.001</td>
<td>0.033</td>
<td>0.011</td>
</tr>
<tr>
<td>Positive mood</td>
<td>204</td>
<td>0.008</td>
<td>0.000 -0.017</td>
<td>0.061</td>
<td>0.032</td>
</tr>
<tr>
<td>Negative mood</td>
<td>204</td>
<td>-0.003</td>
<td>-0.009 -0.002</td>
<td>0.259</td>
<td>0.143</td>
</tr>
<tr>
<td>Social support</td>
<td>201</td>
<td>0.007</td>
<td>-0.002 -0.016</td>
<td>0.120</td>
<td>0.118</td>
</tr>
</tbody>
</table>
Overview of EMA Study
Ecological Momentary Assessment (EMA) study at UCI
(N=250 mothers)

- Baseline Blood/ Hair Sample
- Fasting Blood sample
- Psychosocial Stress Assessment
- Neuropsychological Battery
- Fetal Ultrasound
- Cervicovaginal Swabs
- Anthropometric Measures
- 4 Day Ambulatory Period:
  - Diurnal Salivary Cortisol (7 per day)
  - Actihart Device (beat to beat heart rate)
  - Electronic Diary (Smart Phone)
  - 3 x 24-hr Dietary Recall Assessments
  - 24 hr Urine

- 2-4 weeks:
  - Newborn Body Composition (DXA)
  - Total Energy Expenditure
  - Blood, Saliva, Hair Samples
  - Infant Cognitive, Motor & Emotional Behavior
  - Infant Motor Performance (TIMP)

- Pre-pregnancy BMI

- 6 Months:
  - Infant Body Composition (DXA)
  - Total Energy Expenditure
  - Anthropometrics
  - Blood, Saliva, Hair Samples
  - Infant MRI (brain: structural MRI, DTI, resting state fMRI; body: whole body scans, brown fat scans)
  - Infant Cognitive, Motor & Emotional Behavior (Bayley’s)
  - Infant Stress reactivity (Still face, saliva and heart rate)
  - Maternal sensitivity (stand. Play situation)

- 12 Months:
  - Infant Body Composition (DXA)
  - Total Energy Expenditure
  - Anthropometrics
  - Blood, Saliva, Hair Samples

Metabolomics
- Glycemic parameters
- Inflammatory cytokines

Gestational Period:
- 10-12 Weeks Gestation
- 20-22 Weeks Gestation
- 30-32 Weeks Gestation
- Birth
- 6 Months
- 12 Months

Delivery:
- Placenta, cord blood and cord tissue (telomere biology)
- Newborn Body Composition (DXA)
- Total Energy Expenditure
- Blood/ Saliva Samples
- Anthropometrics
- Neonatal MRI (brain: structural MRI, DTI, resting state fMRI; body: whole body scans, brown fat scans)
- Infant Cognitive, Motor & Emotional Behavior
- Infant Motor Performance (TIMP)
- Infant Body Composition (DXA)
- Total Energy Expenditure
- Anthropometrics
- Blood, Saliva, Hair Samples
- Infant MRI (brain: structural MRI, DTI, resting state fMRI; body: whole body scans, brown fat scans)
- Infant Cognitive, Motor & Emotional Behavior (Bayley’s)
- Infant Stress reactivity (Still face, saliva and heart rate)
- Maternal sensitivity (stand. Play situation)
Role of cytokines in pregnancy

- Placental secretion - mediates normal gestational physiological processes
- Raised pre-pregnancy BMI/adiposity - ↑ inflammatory profile
- Potential effects on:
  - Maternal/fetal insulin resistance via fatty acid / BCAA accumulation
  - Placental AA transport to fetus, may promote excess fetal growth
    (Jones et al., 2006; Jansson et al. 2013)
- Maternal IL-6 in late pregnancy has been associated with increased neonatal adiposity (Radaelli et al., 2007)
Several AA decrease with advancing gestation, including branched chain amino acids (BCAA) leucine & valine
May represent fetal uptake and/or use as gluconeogenic or ketogenic substrates in fasted state

Glutamic acid positively associated, asparagine negatively associated with BMI
Similar associations observed in obese Hispanic children (Butte et al., 2013)
Early pregnancy glutamic acid positively associated with birthweight centile
IL6 significantly associated with pBMI

<table>
<thead>
<tr>
<th>IL-6 measurement</th>
<th>Total cohort N=214</th>
<th>Normal weight (BMI &lt;25.0) N=112</th>
<th>Overweight (BMI 25.0-29.9) N=53</th>
<th>Obese (BMI &gt;30.0) N=46</th>
<th>p-value b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimester 1</td>
<td>0.63 (0.68)</td>
<td>0.47 (0.50)</td>
<td>0.70 (0.54)</td>
<td>1.12 (0.74)</td>
<td>&lt;0.001 §</td>
</tr>
<tr>
<td>Trimester 2</td>
<td>0.67 (0.81)</td>
<td>0.53 (0.61)</td>
<td>0.74 (0.72)</td>
<td>1.13 (0.85)</td>
<td>&lt;0.001 §</td>
</tr>
<tr>
<td>Trimester 3</td>
<td>0.94 (0.80)</td>
<td>0.80 (0.67)</td>
<td>0.79 (0.88)</td>
<td>1.22 (0.93)</td>
<td>&lt;0.001 ¥</td>
</tr>
</tbody>
</table>

p-value a

- <0.001*
- 0.019**
- 0.053

Natural increase in IL6 across gestation

Higher BMI attenuates natural gestational increase

Higher BMI women enter pregnancy with raised IL6
Metabolomic analysis of plasma AA in EMA study

<table>
<thead>
<tr>
<th>Non-essential AA</th>
<th>Essential AA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine</td>
<td>Methionine</td>
</tr>
<tr>
<td>Arginine</td>
<td>Phenylalanine</td>
</tr>
<tr>
<td>Asparagine</td>
<td>Threonine</td>
</tr>
<tr>
<td>Aspartic acid</td>
<td>Tryptophan</td>
</tr>
<tr>
<td>Citrulline</td>
<td>Isoleucine</td>
</tr>
<tr>
<td>Glutamine</td>
<td>Leucine</td>
</tr>
<tr>
<td>Glutamic acid</td>
<td>Valine</td>
</tr>
<tr>
<td>Glycine</td>
<td></td>
</tr>
<tr>
<td>Ornithine</td>
<td></td>
</tr>
<tr>
<td>Cysteine</td>
<td></td>
</tr>
<tr>
<td>Serine</td>
<td></td>
</tr>
<tr>
<td>Tyrosine</td>
<td></td>
</tr>
<tr>
<td>Proline</td>
<td></td>
</tr>
</tbody>
</table>

Branched chain AA
Association of BMI*IL6 interaction with AA metabolites

• Cross-sectional regression models within each trimester:
  
  \[ AA \sim IL-6\times BMI + (IL-6 + BMI + age + ethnicity + OB risk score + smoking) \]

• No significant associations in T1 or T2

• BCAA positively associated in T3

<table>
<thead>
<tr>
<th>Trimester 3 AA</th>
<th>Beta</th>
<th>p-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoleucine</td>
<td>0.026</td>
<td>0.037</td>
<td>0.002</td>
</tr>
<tr>
<td>Leucine</td>
<td>0.033</td>
<td>0.005</td>
<td>0.010</td>
</tr>
<tr>
<td>Valine</td>
<td>0.031</td>
<td>0.012</td>
<td>0.007</td>
</tr>
<tr>
<td>Asparaginine</td>
<td>0.029</td>
<td>0.006</td>
<td>0.011</td>
</tr>
<tr>
<td>Aspartic acid</td>
<td>0.035</td>
<td>0.001</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Insulin resistance and IL-6

• IL-6 across pregnancy +ve correlation with HOMA
  – trimester 1 (r=0.25, p=0.002)
  – trimester 2 (r=0.173, p=0.032)

• But HOMA*IL-6 interaction showed few associations with plasma AA
  – Glutamic acid positively associated in trimester 3 (B=0.093, p=0.038)
  – Not actively transported across placenta
  – Positive association with birthweight centile - fetal programming pathway for obesity?
Summary

**Behavioral level**

- Low quality diet early/mid-pregnancy
  - ↑ Perceived stress
  - ↓ Positive mood
  - ↓ Social support

**Implications for fetal programming of adiposity & metabolic dysfunction**

**Physiological level**

- Raised pre-pregnancy BMI
- Raised IL-6 across pregnancy
  - BMI*IL-6
  - HOMA*IL-6

- ↑ BCAA
  - Implications for fetal programming of insulin resistance

- ↑ Glutamic acid
  - ↑ Birthweight centile
Future Directions

• Long term impact of biological and psychosocial stress on offspring adiposity and metabolic function

• Moderating/mediating effects of prenatal diet on the fetal programming effects of maternal stress

• Specific nutritional components associated with biological and psychosocial stress
Thank you

UC Irvine Development, Health and Disease Research Program, University of California Irvine

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