Neonatal Neurobehavioral Impacts of Iodine Insufficiency and Pesticide Exposures

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History of the project

• 2010 NIH funded 2 year pilot project
• UMass Lowell partnered with Mahidol University Faculty of Public Health in Bangkok Thailand
• Hypothesis: low maternal iodine and pesticide exposure may act synergistically to alter thyroid hormone status resulting in deficiencies in child neurobehavioral development
Methods

• Recruit pregnant women from 3 provinces in Thailand representing a range of risks for pesticide exposure and iodine deficiency disorders.
Methods

– At recruitment (7 months)
  • Urine for iodine & pesticide metabolite (organophosphates (OP))
  • Extensive health history, exposure history, dietary questionnaire

– At birth
  • Urine for maternal iodine, pesticide metabolites (OP’s)
  • Blood for maternal thyroid hormone & hemoglobin levels
  • Placental cord blood for thyroid hormone
  • APGAR and other birth data
  • Brazelton Newborn Behavioral Assessment Survey (BNBAS)
Newborn Behavioral Assessment Scale (NBAS)

- NBAS covers 28 behavioral items and 16 primitive reflexes.
- Cluster scored into 7 domains:
  - habituation,
  - orientation,
  - motor,
  - range of state,
  - regulation of state,
  - autonomic stability,
  - number & type of abnormal primitive reflexes
- Used Certified NBAS trainer to train Thai pediatricians
- Test in first 4 days of life
  - (avg 1.8 days; 91% < 3; max 4)
Further Data Collection

• **Age 2 months**: maternal urine & breast milk for pesticides and iodine & questionnaires

• **Age 5 months**: Neurobehavioral testing with observational Bayley Scales and physiological testing with EEG/ERP (Electroencephalogram/Event Related Potential) & questionnaires

• **Questionnaires**: infant health, behavior, food intake, mothers nutrition and exposure to pesticides
- **EEG/ERP**
  - Infants view images of mother vs stranger (500ms each)
  - EEG/ERP data is collected for 1500 ms after each picture appears on the screen
  - ERP components relate to perceptual processing
- **Bayley Scales**
  - Observational assessment of motor skills (fine & gross) and cognitive development (attention, memory, learning)
    - Mental Development Index
    - Psychomotor Development Index
Unforseen Complications

• In Oct 2010 the MoPH began providing iodine supplement tablets to pregnant women.

• Major flooding Sept 2011-Jan 2012
  – 13.6 million people affected. 65/77 provinces were declared flood disaster zones, > 20,000 km² (7,700 mi²) land damaged, seven major industrial estates flooded to 3 m (10 ft)
Results

- Recruited 112 women at 7 months pregnancy
  - 27 agricultural workers
  - 30 live with agricultural workers or worked in fields less than 1 day per week for only 1 trimester.
  - 55 unexposed to agricultural pesticides
    • 30 (55%) reported applying insecticide in home during pregnancy

- NBAS data collection on 82 newborns
  - 27% loss to follow-up from recruitment due to cesarean section, prematurity (<37 weeks), delivered elsewhere (some due to flooding).
Pesticide Use

Pregnant agricultural workers report:
• 81% used insecticides on their farm
  – 41% used organophosphates
  – 4% report using pyrethroids
• 85% used herbicides on their farm
  – 41% used glyphosate
  – 59% used paraquat
  – 26% use 2,4-D
Pesticide Use

During pregnancy Agworkers reported:
• 19% used pesticides to treat seeds
• 59% mixed pesticides
• 63% applied pesticides to crops
• 37% applied pesticides to animals
• 63% entered fields sprayed with pesticides on the same day
• 74% washed clothes used to mix or apply pesticides (42% wash with regular clothes)
• 57% never use rubber gloves when mixing pesticides
Newborn Behavioral Assessment Scale (NBAS)

- 3/7 Thai test results significantly poorer than CHAMACOS longitudinal birth cohort in California (85% Mexican-American; 64% ≤ poverty level; many agricultural workers)

- 2/7 Thai tests results better than CHAMACOS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Std Dev</th>
<th>Δ CHAMACOS – our data</th>
<th>t-test with CHAMACOS p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Habituation</td>
<td>7.3</td>
<td>1.2</td>
<td>-0.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Orientation</td>
<td>6.1</td>
<td>1.5</td>
<td>1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Motor</td>
<td>5.7</td>
<td>0.8</td>
<td>0.1</td>
<td>0.25</td>
</tr>
<tr>
<td>Range of State</td>
<td>3.9</td>
<td>0.5</td>
<td>-0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Regulation of State</td>
<td>5.2</td>
<td>1.7</td>
<td>0.5</td>
<td>0.003</td>
</tr>
<tr>
<td>Autonomic Stability</td>
<td>6.1</td>
<td>1.1</td>
<td>0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abnormal Reflex</td>
<td>1.8</td>
<td>2.3</td>
<td>-0.1</td>
<td>0.08</td>
</tr>
</tbody>
</table>
– Each NBAS cluster score examined for association with potential covariates in linear or poisson regression (reflex). Covariates included in final model if $p \leq 0.15$

  • Mother’s age, income, education, parity, marital status, alcohol use, cough medicine use, caffeinated soda use, nonprescription medicine use, babies gender, NBAS tester

– Final models include Agworker & Iodine (0/1) variables

  • Agricultural worker (n=21): at least 2-3 days/month in field in any trimester for mother

  • Iodine tablet supplement (n=71): medical staff report of date tablets provided & subject reported receiving tablets during at least 1 trimester.
**Final NBAS Model Estimates**

<table>
<thead>
<tr>
<th></th>
<th>Orientation</th>
<th>Motor</th>
<th>Range of State</th>
<th>Regulation of State</th>
<th>Habituation</th>
<th>Autonomic Stability</th>
<th>Abnormal Reflexes Rel Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Agworker</td>
<td>-0.41 p=0.30</td>
<td>-0.22 p=0.24</td>
<td><strong>0.27 p=0.04</strong></td>
<td>-0.03 p=0.95</td>
<td>-0.45 p=0.10</td>
<td>-0.07 p=0.72</td>
<td>0.77 ChiSq=0.31</td>
</tr>
<tr>
<td>Iodine tablets provided</td>
<td>0.02 p=0.97</td>
<td>0.22 p=0.36</td>
<td>0.17 p=0.34</td>
<td>0.78 p=0.17</td>
<td>-0.24 p=0.55</td>
<td>-0.05 p=0.87</td>
<td>0.45 ChiSq=0.09</td>
</tr>
</tbody>
</table>

- Agworker parameter direction (N.S.) for 5/7 tests suggests being Agworker results in poorer newborn neurological function.
- Iodine parameter direction (N.S.) for 5/7 suggests tablets improve newborn neurological function.
**Newborn Demographics**

- Birth data on 78 of 82 NBAS babies.
- Using linear and logistic regression with covariates: Agworker or iodine tablet supplements were not significant predictors of birth outcomes.

<table>
<thead>
<tr>
<th>Newborn</th>
<th>Mean</th>
<th>SD</th>
<th>% &lt; norm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>3.08</td>
<td>0.41</td>
<td>11</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>51.6</td>
<td>2.3</td>
<td>9</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>22.3</td>
<td>1.4</td>
<td>9</td>
</tr>
<tr>
<td>Apgar 1 min</td>
<td>8.9</td>
<td>1.0</td>
<td>7</td>
</tr>
<tr>
<td>Apgar 5 min</td>
<td>9.7</td>
<td>0.5</td>
<td>5</td>
</tr>
<tr>
<td>Apgar 10 min</td>
<td>9.8</td>
<td>0.4</td>
<td>5</td>
</tr>
</tbody>
</table>
Cord Blood Thyroid Hormone

- 35% of newborns were out of normal TSH range.
  - 6.5% had severely high TSH levels
  - Compared to 4.6% of >5000 neonates at a Bangkok hospital in 2003
- 34% of newborns had low free T4 levels.
- 11.6% newborns clinically hypothyroid based on cord blood
Thyroid Hormone, Iodine supplements & Agworker status

- Using linear and logistic regression with covariates: Agworker or iodine tablet supplements were not significant predictors of thyroid levels or hypothyroid status of either the mother or newborn cord blood.
EEG/ERP

• The latency and amplitude differences for the ERPs suggest slower processing of novel stimuli (stranger’s faces) from the infants of agricultural workers.

• Single child of an agricultural worker who did not receive iodine supplementation showed no discernible ERP components, suggesting very delayed development.
Future Directions

• For NBAS, Thyroid hormone, Birth data
  – Add organophosphate (OP) urinary metabolite levels at 7 months and birth to models
  – Add estimates of iodine uptake from food frequency questionnaire and tablet intake

• Complete collection/analysis of Bayley & EEG/ERP:
  – OP urine metabolite & breast milk levels

• Increase power by recruitment in follow-up study
• Follow subjects longitudinally
• Examine herbicide exposures