Neonatal Nutrition, Epigenetics, and Childhood Obesity

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Percentage of U.S. Children and Adolescents Who Were Overweight*

<table>
<thead>
<tr>
<th>Year</th>
<th>Ages 6-11</th>
<th>Ages 12-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>1963-70</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>1971-74</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>1976-80</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>1988-94</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>1999</td>
<td>6</td>
<td>9</td>
</tr>
</tbody>
</table>

* > 95th percentile for BMI by age and sex based on 2000 CDC BMI-for-age growth charts
** Data are from 1963-65 for children 6-11 years of age and from 1966-70 for adolescents 12-17 years of age

Source: National Center for Health Statistics

US Per Capita High Fructose Corn Syrup Consumption

Obesity is a Genetic Disease

An important and unresolved question:

What role does an organism’s environment play in its development and evolution?
The role of the environment has been underplayed in developmental biology. Developmental biology largely ignores “nongenetic” causes of individual variation. Yet, it is clear that the environment can exert a strong influence on development; e.g., developmental plasticity:

- Clones of Daphnia
  - Reared in the absence of predators
  - Reared in the presence of predators

Daphnia can develop spines in the presence of predators. Spine development is induced by chemicals released by predators (kairomones). Once it has occurred, it is transmitted through the egg (“Transgenerational induction of defenses in animals and plants” Nature 401:60-63). This effect lasts for several generations.

The effect of the environment can be transgenerational.

What is the role of the intrauterine environment?

In the beginning (1989)...

- Data were used to calculate relative risk of developing ischemic heart disease according to weights

Hertfordshire Cohort

Meticulous midwifery records from early 1900s enabled cohort follow up.

Association of Birthweight with Raised Blood Pressure in Hertfordshire Population

Fall et al, BMJ 1995
Birth Weight and Insulin Resistance Syndrome

The Dutch Hunger Winter 1944/1945
400-800 calories/day

The Importance of Timing: the Dutch Hunger Winter

- Operation Market Garden: Allies invaded France in 6/44
- Entered Holland on 9/14/44.
- Failed to cross the Rhine to the north.
- Dutch government called for a rail strike.
- Germans ordered ban on food transport in reprisal for Dutch resistance.
- Severe winter started early.
- Food stocks ran out rapidly.

The Dutch Famine: Rations

- 12/43-10/44 1800 kcal
- 10/44-11/44 1400
- 11/44-4/45 400-800
- 6/45 >2000
- Pregnant and lactating women given an extra amt of food but not during famine’s peak
- Children <1 year locked at 1000 kcal rations.

The Dutch Famine 1944-45 (Historical Cohort Study)

- Exposure to famine in mid or late gestation
  - impaired glucose tolerance
- Exposure to famine in early gestation
  - atherogenic lipid profile
  - obesity
  - increased risk of CHD
  - dissociation with birthweight

Human Epidemiology

- Being exposed to famine during pregnancy or being SGA confers a lifetime risk of diabetes and obesity, independent of genetic background.
- Thought that the body was epigenetically programmed with a “thrifty” phenotype that was adaptive in times of nutritional deprivation, but maladaptive in times of nutritional excess.
- While a useful demonstration of epigenetics in the human, it does not address our current problem...
What effect does maternal diet and metabolic status have on the development of obesity and its complications in the child?

Do GDM affect fetal fat mass?
- Catalano et al studied the infants of 195 GDM pregnancies and 220 controls.
- GDM was well-controlled and there was no difference in final birth weight or fat free mass.
- Statistical differences persisted after controlling for maternal height & weight, gestational age, smoking status, race, paternal weight, and after excluding macromosomic infants.

Weight Gain During Pregnancy

Data from 2012 Mother/Infant Pairs

Mean BMIs in Pima Siblings Exposed and Not Exposed to Diabetic Intrauterine Environments

P = 0.003, controlled for sibship by analysis of variance

Diabetes Prevalence in Pima Children

Does GDM affect fetal fat mass?

Body Composition (by TOBEC)

<table>
<thead>
<tr>
<th></th>
<th>GDM (n = 195)</th>
<th>NGT (n = 220)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFM (g)</td>
<td>2902 ± 405</td>
<td>2975 ± 408</td>
<td>.74</td>
</tr>
<tr>
<td>Fat mass (g)</td>
<td>436 ± 206</td>
<td>362 ± 198</td>
<td>.0002</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>12.4 ± 4.6</td>
<td>10.4 ± 4.6</td>
<td>.0001</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD.
Risk of obesity: “Trouble At Both Ends of the BW Spectrum”

Nutrient Restriction

- Insulin resistance
- Lipolysis
- Micronutrient Deprivation

Obesity / Overnutrition

- Adipokines
- Fatty Acids
- Insulin resistance

INFLAMMATION

Epigenetic Programming of Insulin Resistance & Susceptibility to the Metabolic Syndrome

Maternal Diet and Fetal Liver Disease: Translational Research at OHSU

Maternal Diet Produces an Inflammatory Lipid Profile

Table 1. Total plasma fatty acid levels from NHP mothers, and the fetal blood.

<table>
<thead>
<tr>
<th></th>
<th>Maternal</th>
<th>Fetal</th>
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<tbody>
<tr>
<td>Saturated Fatty Acids (μmol/L)</td>
<td>3071±318</td>
<td>3475±390</td>
</tr>
<tr>
<td>Monounsaturated Fatty Acids (μmol/L)</td>
<td>1171±104</td>
<td>991±196</td>
</tr>
<tr>
<td>n-6 Fatty Acids (μmol/L)</td>
<td>1326±65</td>
<td>1654±294</td>
</tr>
<tr>
<td>n-3 Fatty Acids (μmol/L)</td>
<td>78±4**</td>
<td>268±82</td>
</tr>
<tr>
<td>n-6/n-3 ratio</td>
<td>17±3.1**</td>
<td>7.1±1</td>
</tr>
</tbody>
</table>

Results are mean ± SD. *p<0.05, **p<0.005 vs. control

Fetal Liver Disease at G130

Lipid

Oxidative Stress (HNE)
Out of the Uterus and Into the Fire: Adiposity Rebound

“Adiposity Rebound”

Early Adiposity Rebound and Body Fat
Taylor et al, Obes Res 2004

Infant Weight Gain

Is the Opposite True?

- N=300,000 Dutch military inductees at age 19
- Famine exposure in first 2 trimesters lead to 80% higher prevalence of overweight (p<0.0005)
- Famine exposure in first 5 months of life associated with 40% lower prevalence of overweight (p<0.005)

Summary
- Much of human brain growth and development occurs ex utero, particularly in premature infants.
- Rapid weight gain in early infancy and early adiposity rebound are associated with the development of childhood and adult obesity.
- What factors determine rapid weight gain and adiposity rebound?
Does Breastfeeding Make a Difference?

Breastfeeding and Childhood Obesity

Owen et al. Pediatrics 2005

...and the risk was less with time breastfed

Von Kries et al BMJ 1999

Breastfeeding (BF) Reduces Risk of Diabetes

Among Pima Indians, being BF > 2 months is related to less risk for developing diabetes by 40 years of age

Prevalence of Diabetes

Petitt et al Diab Care 1998

So, in summary

There is strong evidence that:

- Breastfed babies are less likely to grow up as obese children
- Breastfed babies are less likely to develop diabetes and hypertension as young adults

A Cautionary Note...

- Among Pima Indians, being BF > 2 months is related to less risk for developing diabetes by 40 years of age

Prevalence of Diabetes

Petitt et al Diab Care 1998

1958 Was a Good Vintage for Breast Milk
What About 2012 Breast Milk?

- Fructose
- High Fat
- Growth Factors
- Cytokines
- Leptin
- Adiponectin

Is breastmilk altered by diet?

Diet influences the quality but not quantity of breast milk

Type of fat in breast milk is highly sensitive to diet

Fat Content of Breast Milk Increases with Maternal Obesity

Impact of “Diabetic Breast Milk”

- Study of 112 infants of diabetic mothers (approximately half type 1)
- All encouraged to breast feed. Infants supplemented with banked breast milk as needed. Infants then studied with OGTT and body mass at 2 yr. of age.
Summary

- Early infant weight gain and adiposity rebound are associated with adult obesity.
- Historically, breast milk has been protective against the development of obesity and its complications.
- Breast milk constituents are altered by maternal intake and ponderosity.
- Many hormones and nutrients found in breast milk are known to influence the development and function of the brain and the gut.

What is the Influence Maternal Intake on Childhood Flavor Preference?

Infant Flavor Preference is Altered by Maternal Diet

Mennella et al, Pediatrics 2001

Some parting thoughts on early nature vs. nurture in childhood nutrition...
Most Human Behaviors Including Eating are Learned and Influenced by Our Culture

Important Developmental Points in Childhood Feeding

- Some foods are always preferred
- Reward increases food preference
- “Stashing” increases food preference
- A new food must be introduced at least 10 times to be accepted
- Bribery decreases food preference
- Masking decreases food preference
- Children learn to eat by example - this is like language
- A child must be offered the opportunity to eat, and the opportunity to refuse to eat

Thank You!