Early Life Nutrition and Diabetes
In-Utero Stressors and Vulnerability for Chronic Disease

Indian Health Service Diabetes Group
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What is ‘Developmental Programming’?

**Basis:** Biologic capacity of normal *developing* organisms to be *durably* changed by environmental exposures without change in the inherited genome.

**Exposures:** Nutrients, stress, O2, chemicals/toxins

**Mechanisms:** Change in organ structure/function, change in gene expression via epigenetics

**Susceptibility:** Fetus>>infant>>child>>teen>>adult

**Impact:** Vulnerability to development of chronic disease later in life.
We Are What We Eat – And So Are Our Kids & Grand-Kids

Nutritional Life of the Egg is Trans-Generational
Adverse Exposures in Utero

- **Undernutrition**
  - Low Prot
  - Low Calorie
  - Abnormal Fetal Growth (slow/asymmetric)

- **HiCal Malnutrition**
  - Obesity/HiFat
  - Gest’1 DM
  - Abnormal Fetal Growth (fast/asymmetric)

- **Psychosocial Stress**
  - Vulnerability

- **In Utero**
  - ± Environmental Stressors
  - Chronic Disease in Children and Adults
    - Metab Syndrome: Obesity - Diabetes - HTN - CKD
    - Behavioral/Mental/Cognitive Deficits

- **Birth**

- **Childhood**

- **Adulthood**
Biology of Developmental Programming Outline

• The Origins of Developmental Origins: A Paradox
• Evolving History: Lessons from Cohort Studies
• Biological Pathways of Disease Vulnerability
  • Change in organ structure
  • Change in homeostatic system setpoints
  • Interactions of prenatal and postnatal exposures
• Transgenerational Transmission of Disease Risk
  • Mom’s early-life undernutrition affects future baby
  • Mom preconception obesity affects future baby
The Origins of Developmental Origins Socioeconomic Health Disparity

Red areas:
- poor land
- sparse food
- Urban poverty

Green areas:
- rich land
- abundant food
- Non-$ wealth

Neonatal Mortality in early 1900’s has identical pattern

History of Development Programming
“The Paradox”

• Everyone ‘knew’ that Coronary Artery Disease was a disease of societal affluence.
• How then can Coronary Mortality be tracking with socioeconomic disadvantage?

**Answer**: Babies developing in adverse conditions are uniquely susceptible to negative impacts of affluence (hi animal protein, fat, sugar, calories) on chronic disease risk
A Link to Health Disparity

Developmental Programming

- First recognized because it led to socioeconomically-based health disparity
- Is a major *mechanism* by which
  - SE/psychosocial disadvantage becomes *biologically embedded* within a population
  - developmentally-based health disparities can be transmitted to future generations
The Barker Hypothesis
Developmental Origins of Disease

Lessons from Cohort Studies

The British Cohorts
- Small English Villages
- Two time points: Birth
  50+ years

Poor Fetal Growth Increase Risk of Chronic Disease Later in Life
Poor Fetal Growth - Increased Risk of Disease

Hypertension

Coronary Disease & Stroke

Risk of Glu Intol or Diabetes
Birth Weight is Crude Surrogate for Fetal Growth

Asymmetric Growth Restriction

- Thin (Low weight to height ratio)
- Fetal blood flow redistribution
  - Low kidney, lower pancreas
  - Low abdominal girth
  - Heart/brain ‘sparing’
- Low arm circumference (low muscle mass)

May Occur with Normal Birth Weight!
Developmental Origins of Health & Disease

“DOHaD”

? DOUGH HEAD ?

Relatively Large Head (brain sparing)

Abdominal Obesity (central fat)
Developmental Origins of Chronic Disease

- Obesity
- Type II Diabetes
- Hypertension
- Kidney Disease
- Dyslipidemia
- Ischemic Heart Disease
- Osteoporosis
- Asthma/Allergies
- Depression, Anxiety
- ADHD, Schizophrenia
- Breast, Ovarian, & Lung Cancers
Developmental Origins of Disease
Pathways of Nutritional Programming

• Altered organ structure during development
• Altered regulatory system function
• Adverse interaction of prenatal vulnerabilities with postnatal stressors
Programming by Maternal-Fetal Undernutrition
Pathways of Nutritional Programming
Altered Organ Structure/Function
### Pathways of Nutritional Programming

**Structural Deficits – Decreased Number Functional Units**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Structural Deficit</th>
<th>Functional Deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>Decreased Nephron Number</td>
<td>HTN, renal disease</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Decreased Islet β cell Number</td>
<td>Change Insulin secretion</td>
</tr>
<tr>
<td>Muscle</td>
<td>Decrease muscle mass</td>
<td>Decreased Basal met rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased exercise capacity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased insulin sensitivity</td>
</tr>
<tr>
<td>Heart</td>
<td>Decreased myocyte number</td>
<td>Increased Risk CHF</td>
</tr>
<tr>
<td>Liver</td>
<td>Decreased lobule, cell number</td>
<td>Change lipid/protein metab</td>
</tr>
<tr>
<td>Vascular</td>
<td>Decreased microvasc dens</td>
<td>Increased vasc resistance</td>
</tr>
<tr>
<td>Brain</td>
<td>Change neural circuits</td>
<td>Increased appetite, HPA axis</td>
</tr>
</tbody>
</table>
New Nephrons Form in Concentric Layers During Gestation

Condensing Mesenchyme

Comma Shaped Bodies

Glomerul

Outer Nephrogenic Layer

Branching Morphogenesis $\rightarrow$ Nephrogenesis
Reduced Glomerular Number in Human IUGR

Developmental Origins of HTN
Pathways of Nutritional Programming

• Altered Organ Structure during Development
  • Kidney: Decreased nephron number

• Altered Regulatory System Function
  • Energy Balance: “thrifty phenotype”

• Interaction of prenatal vulnerabilities with postnatal stressors
Altered Regulatory System Function in Programmed Offspring
Enhanced Responses to Postnatal Environment*

- Stress hyperreactivity: HPA Axis, cortisol
- Sympathetic nervous system hyperactivity
- Oxidative stress/Inflammatory responses
- Immune hyperactivity (asthma, allergies)
- Change energy homeostasis: Fat, glucose/insulin metabolism, appetite regulation

*Shown with all 3 major programming forces
Altered Energy Homeostasis in Programmed Offspring
“The Thrifty Phenotype”

• The fetus adapts to nutrient deficit by permanently
  • Increasing energy utilization efficiency
  • Increasing appetite – promoting circuits
  • Promoting survival in utero
• These permanent adaptations:
  • Enhance postnatal tolerance to famine
  • Impair ability to handle nutrient excess
• Example: “Rural-to-Urban Transition”

Hales & Barker, 2001
“The Thrifty Phenotype”
What is the Impact of Thrifty Phenotype?

Lessons from Cohort Studies

The Helsinki Cohorts

• Finnish public health records
• Annual child growth data: birth – 15 years
• Adult Outcomes: med Rx, hospital records

Accelerated Postnatal Growth Enhances Risk of Chronic Disease Later in Life
Rapid Early Growth Predicts Adult HTN

Growth Patterns in 1404 Children who later developed Hypertension

- **BMI**
- **Weight**
- **Height**

Cohort Average (n=8760)

Barker et al. J HTN 20: 1951, 2002
Rapid Early Growth Patterns Predict Adult HTN ± Diabetes

Early Growth Patterns in Low-Birth-Wt Women with later Adult-onset Hypertension

Eriksson et al, Hypertension 2000
Prevalence of Metabolic Syndrome
Crossing Percentiles Enhances Disease

Valdez et al 1994
Early Growth Patterns Predict Adult HTN

Adverse Impact of Accelerated Growth
Born Small + Rapid Childhood Growth

Risk of Coronary Disease in
Men Born Thin ± Rapid Childhood Growth

Ericksson et al 2001
Developmental Origins of Cardiovascular Disease

- Fetal Under-Nutrition
  - Altered Birth Phenotype
    - Vulnerability
      - Food
      - Low SES
        - ↑ Postnatal Growth
          - Cardio/Renal/Metabolic Disease
            - HTN
            - Abd’I Obesity
            - Renal Disease
            - Diabetes
            - ↑TG/↓HDL
            - Cor Art Dis
Developmental Origins of HTN
Pathways of Nutritional Programming

• Altered Organ Structure – Change Function
  • Kidney: Decreased nephron number

• Altered Homeostatic Setpoint
  • Energy Balance: “thrifty phenotype”

• Adverse interaction of prenatal vulnerabilities with postnatal stressors
What Conveys Risk of HTN-Renal Disease in Lower Birth-Weight Offspring?

Low Nephron Number?

1Am J HTN 1988 1:335-47;
2Am J Kid Dis 1994 23: 171
Programming Pathways: Mismatch

Early Asymmetric Growth Restriction

\[ \Delta \text{Energy Homeostasis} \]
- "Thrifty Phenotype"
  - Hyperphagia
  - \( \downarrow \) Locomotor Activity
  - \( \uparrow \) Energy Utilization Efficiency

\[ \Delta \text{Renal Development} \]
- \( \downarrow \) # Nephrons
  - FIXED LOW
  - Excretory Capacity

**FOOD**

Accelerated Growth

\( \uparrow \) BODY MASS

Low Excretory Capacity

\( \downarrow \) # Nephrons

\( \uparrow \) HTN & Renal Risk
Mismatch

END STAGE RENAL DISEASE (ESRD)
Dialysis or Transplant

High Cardiovascular Risk

Chronic Kidney Disease (CKD)
Reduced GFR (late stage)

HTN

Progressive nephron loss;
Fewer and fewer functional nephrons remain

Focal Glomerular Sclerosis (FSGS)
Poor Fetal Growth Affects ESRD Risk

Adapted from: Lackland D et al. Arch Intern Med, 2000
Biology of Developmental Programming

Outline

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Transgenerational Transmission of Programmed Changes

Nutritional Life of the Egg is Trans-Generational

GrandMother  Mother  Daughter
Transgenerational Transmission of Programmed Disease Risk

A Mother’s Lifetime Preconception Exposures Impacts *Future* Pregnancies

- **Undernutrition** in mom’s early life:
  - Limits metabolic capacity to nurture future fetus
    - increased Amino Acid oxidation
    - reduced protein turnover rate
  - Impairs future fetal, childhood growth
    Links with offspring hypertension, obesity

- **Undernutrition** in the preconceptual period
  - Links with hypertension in adult offspring
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“Double Burden” of Malnutrition

In Utero
- Undernutrition
  - Low Prot
  - Low Calorie
- HiCal Malnutrition
  - Obesity/HiFat
  - Gest'l DM

Birth
- Abnormal Fetal Growth (slow/asymmetric)
- Abnormal Fetal Growth (fast/asymmetric)

Vulnerability
- Environmental Stressors

Childhood

Adulthood

Chronic Diseases in Children and Adults
- Metabolic-Cardiovascular-Renal
Obesity Risk in Offspring of Obese Mothers
Maternal Obesity/High Energy Diet

Eriksson J et al InternatI J Obesity 2001
Consequence of Maternal Obesity for Offspring

Obstetric Risks
- Pre-Eclampsia
- Gestational DM
- Prematurity
- Congenital malformations

Offspring Outcomes
- LGA/Macrosomia
- IUGR
- Insulin resistance
- Rapid infant growth
- Early-onset obesity
- Early-hypertension
- Early-diabetes
Maternal Hi Fat Diet/Obesity Programming Effects in Monkey Offspring

• Fetal/Neonatal Liver:
  • Fat deposition (hepatic ‘lipotoxicity’)
  • Inflammation, oxidative stress
  • Fatty liver disease (neonate)

• Fetal Brain:
  • Inflammation
  • Change neural appetite circuits, reward center setpoints

• Postnatal Behaviors:
  • Increased appetite (hyperphagia)
  • Preference for hi fat/sweet/salty food
  • Accelerated infant growth rate
  • Early excess adiposity (age 6 mo)
  • Early onset puberty
  • Increased Anxiety (females)/Aggression (males)

Grove K et al: Non-human primate model (ONPRC)
Fetal Liver Fat Accumulation/Lipotoxicity in Offspring of Monkey Mom’s on Chronic High Fat Diet
Maternal Obesity & Risk of Behavioral Dysfunction

Children’s ADHD and Executive Function Scores Based on Mother’s Body Mass Index

Buss C et al. PLoS One, June 2012
“Double Burden” Malnutrition

- Nutritional Adversity
  - Undernutrition: Low Prot, Low Calorie
  - HiCal Malnutrition: Obesity/HiFat, Gest'I DM

- Vulnerability
  - Rapid Childhood Growth
  - Rapid Infant Growth

- Childhood-Onset
  - Metabolic-Cvasc-Renal Disease
Obesity-Hypertension in Children/Adolescents
Transgenerational Transmission
Metabolic Syndrome in 6 Year Old Offspring Predicted by Maternal Pre-Pregnancy BMI

The Generation R Study: Hypertension 2014;63:683-691
Rising Prevalence of Maternal Obesity
Impact of Neighborhood Socio-Economic Status

Sellstrom E et al, BMC Pregnancy and Childbirth, Sweden, 2009
Adverse Exposures in Utero

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- Vulnerability
  - ± Environmental Stressors

- Chronic Disease in Children and Adults
  - Metabolic-Cardiovascular-Renal Disease
  - Behavioral/Mental/Cognitive Deficits
What Do We Do About All This??

Think Trans-generational

A girl is a **mother** form the time of her own mother’s conception.

A mother is the biological bridge to the health of future generations.
Transgenerational Transmission of Programmed Changes

Key Populations at Risk:
Young girls, moms-to-be, pregnant women, young families
Protecting Future Generations

It Takes a Village...

Crucial Elements

• Healthy food choices for girls, young women, young families
• Support from husbands, partners, community
• Renewal of food wisdom in family, community, schools
• Regulation of inappropriate marketing to youth
• Restore “FOOD VALUE” - Put our $$ in our youth’s mouths
The Bob & Charlee Moore Institute for Nutrition and Wellness

Mission
To reduce the prevalence of chronic diseases across the lifespan

- In current and future generations
- Via promoting healthy, nutrient-rich whole-food diets in early life
  - Before conception
  - During pregnancy and lactation
  - In infancy and early childhood

The Power of Partnership
Identifying At-Risk Groups
Practical Suggestions for Clinicians

• Include at-risk babies, children, moms, families
• Document obstetric history in chart
  • Mom: obesity, hi fat diet, GDM, preeclampsia
  • Offspring: birth wt/length, prematurity, gest’l age
• Track infant/childhood size, growth rate
• Recognize growth centile crossing as indicator of metabolic stress, higher disease risk
• At-risk children need regular monitoring
  • BP monitoring/tracking
  • Referrals for food insecurity, for obesity
  • Family referrals for nutrition education
We Are What We Eat – And So Are Our Kids & Grand-kids

Transgenerational Transmission of Chronic Disease Risk
Maternal Stress Causes Stress-Hyperactivity in Programmed Offspring
Enhanced Reactivity to Postnatal Environment

Maternal Stress: poverty, discrimination, fear, perceived lack of control

Offspring Phenotype:

- Low birth weight (due to high fetal cortisol)
- Increased cortisol response to pain, social stress, public speaking
- Impaired cognition (verbal, memory)
- Increased aggression, rule-breaking, ADHD
- Increased metabolic dysfunction

Review: Reynolds R. Psychoneuroendocrinology 38: 2013
Maternal Glucose Elevations Convey Graded Offspring Risk in NonDiabetic Pregnancy

- 25,505 pregnant women
- Tested 24-32 weeks

**Outcomes**

Graded increase in:
- LGA babies
- Cord blood C-peptide
- Primary C-Section
- Neonatal hypoGly

The HAPO Study. NEJM May 2008
Rapid Childhood Growth Predicts HTN
Helsinki Cohort

Cumulative % HTN: BWt vs △ BMI
over 3-11 Yrs

Rapid Childhood Growth Predicts HNT & Enhances Birth Weight Effects

Helsinki Cohort: Random Sample

Avg Age 62 yrs
n = 2003

% Prevalence
HTN