A Life Course Perspective: Overview of Theory

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Western MCH Nutrition Leadership Network
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“If you want 1 year of prosperity, grow grain. If you want 10 years of prosperity, grow trees. If you want 100 years of prosperity, grow people.”

Chinese Proverb
“If you want to grow healthy people, you start by improving MCH nutrition.”

Not A Chinese Proverb
Life-Course Perspective

- A way of looking at life not as disconnected stages, but as an integrated continuum
Life Course Perspective

Life Course Perspective

- Early programming
- Cumulative pathways
- Implications for MCH Nutrition Leadership
Early Programming
Barker Hypothesis
Birth Weight and Hypertension

Barker Hypothesis
Birth Weight and Insulin Resistance Syndrome

Maternal Stress & Fetal Programming
Prenatal Stress & Programming of the Brain

- **Prenatal stress (animal model)**
  - **Hippocampus**
    - Site of learning & memory formation
    - Stress down-regulates glucocorticoid receptors
    - Loss of negative feedback; overactive HPA axis

  - **Amygdala**
    - Site of anxiety and fear
    - Stress up-regulates glucocorticoid receptors
    - Accentuated positive feedback; overactive HPA axis

Prenatal Programming of the Hypothalamic-Pituitary-Adrenal Axis

Epigenetics

VOLUME CONTROLS FOR GENES

THE DNA SEQUENCE is not the only code stored in the chromosomes. So-called epigenetic phenomena of several kinds can act like volume knobs to amplify or mute the effect of genes. Epigenetic information is encoded as chemical attachments to the DNA or to the histone proteins that control its shape within the chromosomes. Among their many functions, the epigenetic volume controls muffle parasitic genetic elements, called transposons, that riddle the genome.

1 Chemical changes to a chromosome can force some parts of it to condense into a tight, inaccessible mass or can recruit repressor proteins. In both cases, the genes on that part of the DNA temporarily stop working.

2 Chromosomes are made of chromatin, a mélange of DNA, proteins and other chemicals. Inside a chromosome, the double helix loops around spools of eight histone proteins to form a rosary-like chain of nucleosomes.

3 An intricate histone code—written in chemical tags stuck to the histones' tails (above)—governs gene expression as well. Acetyl tags usually amplify nearby genes, whereas acetyl-removing enzymes mute them. But the rest of the code remains to be deciphered.

4 Genes can also be suppressed by methyl tags that stick directly to the DNA, usually at places where a C base is followed by a G. Whether DNA methylation turns down genes independently or only in combination with histone tags is still a mystery.

5 Transposons, also called jumping genes, can clone themselves and then insinuate the copies into distant sections of the genome, sometimes disabling or hyperactivating genes. One major function of DNA methylation seems to be the suppression of transposons, which make up almost half the human genome.

Gibbs WW. The Unseen Genome: Beyond DNA. Scientific American 2003
Epigenetics
Same Genome, Different Epigenome

Prenatal Programming of Childhood Obesity
Epidemic of Childhood Overweight & Obesity

Source: National Center for Health Statistics, National Health and Nutrition Examination Survey

Note: Estimate not available for 1976-1980 for Hispanic; overweight defined as BMI at or above the 95th percentile of the CDC BMI-for-age growth charts
Prenatal Programming of Childhood Overweight & Obesity

Jennifer S. Huang - Tiffany A. Lee - Michael C. Lu

Abstract. Objective: To review the scientific evidence for prenatal programming of childhood overweight and obesity, and discuss its implications for MCH research, practice, and policy.

Method: A systematic review of observational studies examining the relationship between prenatal exposures and childhood overweight and obesity was conducted using MOOSE guidelines. The review included literature posted on PubMed and MDC results and published between January 1975 and December 2008. Prenatal exposures to maternal diabetes, malnutrition, and cigarette smoking were examined, and primary study outcome was childhood overweight or obesity as measured by body mass index (BMI) for children ages 5 to 21.

Results: Most of the included studies of prenatal exposure to maternal diabetes found higher prevalence of childhood overweight or obesity among offspring of diabetic mothers, with the highest quality study reporting an odds ratio of adolescent overweight of 1.4 (95% CI 1.0-1.9). The Dutch famine study found that exposure to maternal malnutrition in early, but not late, pregnancy was associated with increased odds of childhood obesity (OR 1.9, 95% CI 1.5-2.4). All eight included studies of prenatal exposure to maternal smoking showed significantly increased odds of childhood overweight and obesity, with most odds ratios clustering around 1.5 to 2.0. The biological mechanisms mediating these relationships are unknown, but may be partially related to programming of insulin, leptin, and ghrelin/ghrelin resistance in sperm.

Conclusion: Our review supports prenatal programming of childhood overweight and obesity. MCH research, practice, and policy need to consider the prenatal period a window of opportunity for obesity prevention.

Keywords: Prenatal programming - Childhood obesity - Overweight - Developmental programming - Fetal programming - Gestational diabetes - Maternal malnutrition - Cigarette smoking

Childhood overweight and obesity is a growing problem in the United States and worldwide. The prevalence of child- overweight in the U.S. tripled between 1980 and 2000 (11). Today approximately 1 in 6 (16%) U.S. children are overweight with significant racial-ethnic disparities. For example, nearly 1 in 4 (25%) non-Hispanic black girls ages 6 to 19 are overweight, a prevalence almost twice that of non-Hispanic white girls (11).

Overweight and obesity has significant lifelong consequences on the health and well-being of children. Childhood obesity is associated with early-onset Type II Diabetes mellitus, hypertension, metabolic syndrome, and sleep apnea. It is also associated with cognitive and intellectual impairment and social exclusion and stigmatization as parts of a vicious cycle including school avoidance (3). Childhood obesity tracks strongly into adulthood (4, 5); obesity beyond
Prenatal Programming of Childhood Obesity

- Maternal Diabetes & Intrauterine Hyperglycemia
  - Intrauterine Hyperinsulinemia (Fetal Pancreatic \( \beta \) Cells)
    - Preadipocyte Differentiation
      - Adipocyte Hyperplasia
    - Programmed Insulin Resistance
      - Postnatal Hyperinsulinemia
        - Hypothalamic Leptin Resistance
          - Hyperphagia
            - Hyperinsulinism
              - Adipogenesis
        - Pancreatic \( \beta \)-Cell Leptin Resistance
          - Hyperinsulinism
Cumulative Pathways
Allostasis: Maintain Stability through Change

Allostastic Load: Wear and Tear from Chronic Stress

**Stressed vs. Stressed Out**

**Stressed**
- Increased cardiac output
- Increased available glucose
- Enhanced immune functions
- Growth of neurons in hippocampus & prefrontal cortex

**Stressed Out**
- Hypertension & cardiovascular diseases
- Glucose intolerance & insulin resistance
- Infection & inflammation
- Atrophy & death of neurons in hippocampus & prefrontal cortex
Allostasis & Allostatic Load

Rethinking Preterm Birth
Preterm Birth

- Infant Mortality: 36%
- Neurologic Disabilities: 50%
- Term Births: 12.3%

NCHS 2010
**Racial & Ethnic Disparities**

**Preterm Births < 37 Weeks**

<table>
<thead>
<tr>
<th>Race</th>
<th>Percent of Live Births</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American</td>
<td>17.9</td>
</tr>
<tr>
<td>White</td>
<td>11.5</td>
</tr>
</tbody>
</table>

Year 2010 Goal

NCHS 2006
Racial & Ethnic Disparities
Very Preterm Births < 32 Weeks

Percent of Live Singleton Births

African American: 4.05
White: 1.63

Year 2010 Goal

NCHS 2006
Racial & Ethnic Disparities
Infant Mortality

Deaths Per 1,000 Live Births

African American: 13.7
White: 5.7

Year 2010 Goal

NCHS 2006
Vulnerability to preterm delivery may be traced to not only exposure to stress & infection during pregnancy, but host response to stress & infection (e.g. stress reactivity & inflammatory dysregulation) patterned over the life course (early programming & cumulative allostatic load).
Preterm Birth & Maternal Ischemic Heart Disease

Kaplan-Meier plots of cumulative probability of survival without admission or death from ischemic heart disease after first pregnancy in relation to preterm birth

Smith et al Lancet 2001;357:2002-06
A Life-Course Perspective: Implications for MCH Nutrition Leadership
I. Improving MCH Nutrition
“If you want to grow healthy people, you start by improving MCH nutrition.”

Not A Chinese Proverb
Not Only During Pregnancy, But Before, Between, and Beyond
Periconception

- Preconception
- Conception
- Implantation
- Placentation
- Embryogenesis
- Organogenesis
Periconceptional Nutrition & Infertility

• Nurses Health Study II

• Women with ovulatory infertility
  • Consumed greater amounts of trans fats (Chavarro et al 2007)
  • Consumed greater amounts of low fat dairy foods (Chavarro et al 2007)
  • Consumed greater amounts of carbohydrates (Chavarro et al 2009)
  • Had higher dietary glycemic load (Chavarro et al 2006)
  • Consumed greater amounts of animal proteins & lower amounts of vegetable proteins (Chavarro et al 2008)
  • Were less likely to use iron supplements (Chavarro et al 2006)
  • Were less likely to use multivitamin supplements (Chavarro et al 2008)

• “Fertility diet” associated with lower ovulatory infertility
  • (RR=0.34; 95% CI 0.23-0.48) (Chavarro et al 2007)
Periconceptional Nutrition & Infertility

Periconception Nutrition & Birth Defects

• Folate
  • Periconceptional folate supplementation has a strong protective effect against neural tube defects \((RR=0.28, 95\% \text{ CI: } 0.13, 0.58)\) (Lumley et al Cochrane Database Syst Rev. 2001;(3):CD001056.)
  • Periconceptional folate supplementation may prevent other birth defects (e.g. conotruncal and septal defects; orofacial clefts) (Botto et al Am J Med Genet C Semin Med Genet. 2004;15:12-21)
## Periconception Nutrition & Birth Defects

<table>
<thead>
<tr>
<th>Author</th>
<th>Micronutrients</th>
<th>Condition</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groenen (2004)</td>
<td>Iron, Magnesium, Niacin</td>
<td>Spina bifida</td>
<td>Increased spina bifida with lower dietary intake of iron, magnesium, niacin</td>
</tr>
<tr>
<td>Velie (1999)</td>
<td>Zinc</td>
<td>Neural tube defects</td>
<td>Reduced NTDs with increased dietary &amp; supplement intake of zinc</td>
</tr>
<tr>
<td>Krapelis (2004)</td>
<td>Iron, Magnesium, Ascorbic acid</td>
<td>Orofacial clefts</td>
<td>Reduced OFCs with increased dietary intake of iron, magnesium, ascorbic acid</td>
</tr>
<tr>
<td>Smedts (2008)</td>
<td>Riboflavin, Nicotinamide</td>
<td>Congenital heart defects</td>
<td>Increased CHDs with lower dietary intake of riboflavin &amp; nicotinamide</td>
</tr>
<tr>
<td>Verkleij-Hagoort (2006)</td>
<td>B-vitamins</td>
<td>Congenital heart defect</td>
<td>Increased CHDs with lower dietary intake of vitamin B12</td>
</tr>
</tbody>
</table>

Cetin et al. Role of micronutrients in the periconceptional period. Human Reprod Update 2009;16:80-95
Periconceptional Nutrition
Birth Defects

• Neural crest cells are involved in organogenesis of the neural tube, lip/palate, and heart.

• Migration and differentiation of neural crest cells are influenced by homocysteine.

• Folate and B12 deficiencies have been shown to result in hyper-homocysteinemia.

• Organogenesis begins early.

Cetin et al. Role of micronutrients in the periconceptional period. Human Reprod Update 2009;16:80-95
Periconceptional Nutrition
PTB & SGA

- **Pregnancy Infection, and Nutrition Study**
  - Preconception multivitamin use associated with lower risk of PTB (RR=0.50; 95%CI 0.20, 1.25)
  - prenatal and periconceptional use were not related to PTB

- **Pregnancy Exposures and Preeclampsia Prevention Study**
  - Periconceptional multivitamin use associated with lower risk of spontaneous PTB (<34 weeks) (OR=0.40, 95% CI: 0.16, 0.99) and SGA (<5th percentile) (OR=0.64, 95% CI: 0.40, 1.03) (Catov et al Am J Epidemiol. 2007;166:296-303.)
Periconceptional Nutrition
PTB & SGA

• **FASTER Trial**
  - Preconceptional folate supplementation for 1 y or longer associated with lower risk of spontaneous extreme PTB (20-28 wks) (HR 0.22, 95% CI 0.08-0.61) and early PTB (28 and 32 wk) (HR 0.45, 95% CI 0.24-0.83).

• **Generation R Study**
  - Preconception folic acid supplementation was associated with lower risks for LBW OR 0.43, 95 % CI 0.28, 0.69 & SGA (OR 0.40, 95 % CI 0.22, 0.72) (Timmermans et al Br J Nutr. 2009;102:777-85)
Periconceptional Nutrition & Preeclampsia

- **Pregnancy Exposures and Preeclampsia Prevention Study**
  - periconceptional multivitamin use associated with a 45% reduction in preeclampsia risk compared with nonuse (OR=0.55, 95% CI: 0.32, 0.95) (Bodnar et al. Am J Epidemiol. 2006;164:470-7)

- **Danish Birth Cohort Study**
  - periconceptional multivitamin users had a 22% lower risk of preeclampsia compared to non-users (HR = 0.78, 95% confidence interval: 0.60, 0.99) among normal weight women. (Catov et al. Am J Epidemiol. 2009;169:1304-11)
Periconceptional Nutrition
PTB, SGA, & Preeclampsia

• Major Pathways to Spontaneous PTB (IOM 2007)
  • Premature activation of maternal-fetal HPA axis
    • periconception undernutrition accelerates maturation of the fetal HPA axis (Bloomfield et al Endocrinology. 2004;145:4278-85)
  • Infection/inflammation
    • Nutrition plays an important role in host susceptibility to infection/inflammation
  • Placental complications
    • one-third of PTB the placental bed vessels show failure of vascular remodeling; 15-25% show decidual vascular pathology characterized by thromboses and atheroses.

• Preeclampsia
  • Implantation defects
Spiral Artery (normal pregnant)
Spiral Artery (Preterm)
Periconceptional Nutrition & Implantation/Placentation

- Folate and B12 deficiencies linked to defects in the placental vascular bed

- Folate & B12 deficiencies result in hyperhomocysteinemia, which can cause placental thromboses & atheroses

- Vitamin C, vitamin E, vitamin D, iron, zinc, and other antioxidants protect against oxidative stress

Cetin et al. Role of micronutrients in the periconceptional period. Human Reprod Update 2009;16:80-95
The Role of the Placenta in Fetal Programming

Table 1. Associations between placental weight and the placental weight/birthweight ratio (placental ratio) and long-term cardiovascular and metabolic outcomes

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>Association with later outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small placental weight</td>
<td>↑ adult blood pressure</td>
<td>Campbell et al., 1996</td>
</tr>
<tr>
<td>Small placental weight</td>
<td>↑ adult hypertension with diabetes</td>
<td>Eriksson et al., 2000</td>
</tr>
<tr>
<td>Small placental volume*</td>
<td>↑ childhood blood pressure</td>
<td>Thame et al., 2000</td>
</tr>
<tr>
<td>Large placental weight</td>
<td>↑ adult blood pressure</td>
<td>Barker et al., 1990</td>
</tr>
<tr>
<td>Large placental weight</td>
<td>↑ childhood blood pressure</td>
<td>Low et al., 1991</td>
</tr>
<tr>
<td>Large placental weight</td>
<td>↑ childhood blood pressure (boys only)</td>
<td>Moore et al., 1996</td>
</tr>
<tr>
<td>High placental ratio</td>
<td>↑ adult blood pressure</td>
<td>Taylor et al., 1997</td>
</tr>
<tr>
<td>High placental ratio</td>
<td>↑ adult blood pressure</td>
<td>Barker et al., 1992</td>
</tr>
<tr>
<td>High placental ratio</td>
<td>↑ adult hypertension without diabetes</td>
<td>Moore et al., 1999</td>
</tr>
<tr>
<td>Placental weight/ratio</td>
<td>↑ childhood blood pressure</td>
<td>Eriksson et al., 2000</td>
</tr>
<tr>
<td>Placental weight/ratio</td>
<td>↑ adult blood pressure</td>
<td>Wimaup et al., 1995</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>↑ coronary heart disease (men)</td>
<td>Martyn et al., 1995b</td>
</tr>
<tr>
<td>Placental weight</td>
<td>↑ coronary heart disease (men)</td>
<td>Martyn, Barker &amp; Osmond, 1996</td>
</tr>
<tr>
<td>Placental weight</td>
<td>↑ coronary heart disease (men &amp; women)</td>
<td>Leon et al., 1998</td>
</tr>
<tr>
<td>Placental weight</td>
<td>↑ coronary heart disease (women)</td>
<td>Forsen et al., 1999</td>
</tr>
<tr>
<td>Placental weight</td>
<td>↑ coronary heart disease (men)</td>
<td>Eriksson et al., 2001</td>
</tr>
<tr>
<td>Low placental ratio</td>
<td>↑ coronary heart disease (men)</td>
<td>Martyn, Barker &amp; Osmond, 1996</td>
</tr>
<tr>
<td>High placental ratio</td>
<td>↑ coronary heart disease (men)</td>
<td>Martyn, Barker &amp; Osmond, 1996</td>
</tr>
<tr>
<td>High placental ratio</td>
<td>↑ coronary heart disease (women)</td>
<td>Forsen et al., 1999</td>
</tr>
<tr>
<td>Stroke</td>
<td>↑ stroke death rates</td>
<td>Martyn, Barker &amp; Osmond, 1996</td>
</tr>
<tr>
<td>Glucose tolerance</td>
<td>↑ type-2 diabetes</td>
<td>Forsen et al., 2000</td>
</tr>
<tr>
<td>High placental ratio</td>
<td>↑ prevalence of impaired glucose tolerance</td>
<td>Phipps et al., 1993</td>
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<tr>
<td>Plasma fibrinogen</td>
<td>↑ plasma fibrinogen</td>
<td>Martyn et al., 1995a</td>
</tr>
<tr>
<td>Plasma fibrinogen</td>
<td>↑ plasma fibrinogen</td>
<td>Barker, Osmond &amp; Meade, 1992</td>
</tr>
</tbody>
</table>

*↑Association found in the direction shown; — no significant association found. *Measured in mid-trimester.
Periconceptional Nutrition & Fetal Programming

- Periconceptional nutrition can influence epigenetic modifications in the preovulatory oocyte and/or preimplantation embryo

- In sheep, restricting folate, vitamin B12, & methionine from periconceptional maternal diet leads to widespread epigenetic modifications, increased adiposity, insulin resistance, altered immune function, and high blood pressure in adult offspring
  (Sinclair et al Proc Natl Acad Sci U S A. 2007;104:19351-6)

- In humans, periconceptional folic acid use was associated with increased methylation of the IgF2 gene in the offspring
  (Steegers-Theunissen et al PLoS One. 2009;4:e7845)
Periconceptional Origins of Health and Disease?
II. Improving Healthcare Quality
Prenatal Care 1.0

- Receptionist & Clerks
- Medical Assistant
- Nurse Manager
- Ultrasound Tech
Prenatal Care 3.0

- Genetic Counseling & Prenatal Diagnosis
- Ultrasound Center
- OB Hospitalist
- High Risk OB
- WIC Primary & Preventive Services
- Health/Nutrition Education
- Oral Health
- Family Support & Social Services
- Family Planning
- Specialty Clinics

Medica Home
Prenatal Care 3.0

Nutrition

Reproductive Potential

Medical Home for Women’s Health

Medical Home for Adolescent Health

Medical Home for Pediatric Health

Optimal Health Development

Lower Health Development Trajectory

0 10 20 30 40 Years

Optimal Health Development
III.
Reinvent Public Health
Assure the conditions in which people can be healthy

Lu Ann Aday
Reinventing Public Health, 2005
<table>
<thead>
<tr>
<th>Healthy Food</th>
<th>Housing</th>
<th>Childcare</th>
<th>Medical Care</th>
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<tbody>
<tr>
<td>Parks and Activities</td>
<td></td>
<td></td>
<td>Clean Air</td>
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<tr>
<td>Education</td>
<td>Economic Justice</td>
<td>Preschool</td>
<td>Safe Neighborhoods</td>
</tr>
<tr>
<td>Residents</td>
<td></td>
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<td>Transportation</td>
</tr>
</tbody>
</table>
Best Babies Zones
Eliminate Disparities in Child & Family Health
Close infant mortality gap in 10 years
Whatever It Takes
Best Babies Zone

Economic Development

Educational Development

Community Development

Health Development
If you live in a BBZ, your baby will have access to
Best healthcare
Best education
Best opportunities
Best community
Best Babies Zones

If you live in a BBZ, your baby will have the best chance in life
Best Healthcare

- Preconception & interconception care
- Quality improvement in prenatal & intrapartum care
- Service coordination & systems integration
- “Pipeline to health”
- Cost-control platform
Best Education

- “Baby college”
- Quality early childhood education
- Service coordination & systems integration
- “Pipeline to success”
- Health promotion in schools
Best Opportunities

- Financial literacy & asset development for families ("pipeline to prosperity")
- Service coordination & systems integration in safety net programs
- Microfinance
- Job creation
- Policy & advocacy
Best Community

- “Pipeline to fatherhood”
- Racial equity
- Transform food deserts & obesogenic environment
- Environmental justice
- Policy & advocacy
The definition of insanity is doing the same thing over and over and expecting different results

Benjamin Franklin
"We must become the change we want to see."

- MOHANDAS GANDHI
“Never, ever, think outside the box.”