Developmental Origins of Disease: Opportunities for Early Life Intervention

Rosenie Thelus Jean, Ph.D
Overview

- What is Developmental Origins of Health and disease (DOHaD)?
- Development Origins of Cardiovascular Diseases
- Development Origins of Cancer
  - Illustrative example of Early Life Exposures and Puberty
- Opportunities for Intervention
Leading Causes of Death in the US

- Financial cost estimated at $700 billion or higher in 2010
- Historically, more emphasis on adult risk factors and preventive strategies

CDC/National Center for Health Statistics, 2007
Developmental Origins of Disease

- Barker DJP
  - Fetal and infant origins Hypothesis

- Gluckman and Hanson
  - Predictive Adaptive Response
Cota, BM; Allen, PJ. The Developmental Origins of Health and Disease Hypothesis. Primary Care Approaches. PEDIATRIC NURSING. May-June 2010, Vol. 36, No. 3
Development Origin of Cardiovascular Diseases

_In-utero factors_

- Caloric restriction
  - Stein, AD et al., 2006, EJE

- Gestational diabetes
  - Gillman MW et al., 2003, 2009, 2010

- Preeclampsia
  - Ogland B et al., 2009, 2010
Development Origin of Cardiovascular Diseases

Perinatal and postnatal factors

- Low birth weight and preterm births
  - Stein D et al., 2006

- Infant feeding
  - Michels KB et al., 2007

- Infant growth trajectory
  - Leunissen RW, 2009
Development Origin of Cardiovascular Diseases

*Childhood and adolescence factors*

- Nutrition
- Physical activity
- Natural/built environment
Development Origin of Breast Cancer

*In-utero factors*

- Estrogens
  - DES and breast/uterine cancers

- Preeclampsia
  - Forman MR et al., 2005

- Twins/Race/ethnicity
Development Origin of Cancers

Perinatal and postnatal factors

- High birth weight
  - Michels KB, Forman, MR

- Birth Length
  - Forman MR

- Breast feeding
  - Wise et al., 2009
Development Origin of Cancers
Childhood and adolescent factors

- Obesity
- Age at puberty/menarche
Illustrative Example

Early Life exposure and Puberty as an intermediate outcome
Study: More U.S. girls starting puberty early

By Amanda Gardner, Health.com

STORY HIGHLIGHTS
- Experts aren't sure what's behind the increase in earlier puberty
- Studies showed girls who started puberty earlier at greater risk for certain cancers
- Doctor: Chemicals such as bisphenol-A (BPA) may affect hormones

Pubertal Assessment Method and Baseline Characteristics in a Mixed Longitudinal Study of Girls

AUTHORS: Frank M. Biro, MD, a Maida P. Galvez, MD, MPH,a Louise C. Greenspan, MD, a Paul A. Succop, PhD, a Nita Vangeepuram, MD, b Susan M. Pinney, PhD, b Susan Teitelbaum, PhD, b Gayle C. Windham, PhD, e Lawrence H. Kushi, ScD, f and Mary S. Wolff, PhD b

WHAT'S KNOWN ON THIS SUBJECT: Age of onset of puberty in girls has fallen in the past 2 decades. It is unclear whether this trend is continuing or the age of onset of puberty in girls has stabilized.

WHAT THIS STUDY ADDS: The authors describe the method and comparability of maturation assessment across 3 geographically distinct centers. It seems that age at onset of puberty is continuing to fall in white but not black girls. Black girls continue to mature at younger ages than white girls.
Implications of Earlier age at puberty/Menarche

- Increased risk of breast, and hormonally driven cancers
- Increased risk of smoking and drinking in adolescence
- Increased risk of emotional and psychological problems
Stages of puberty

- Five stages known as Tanner Stage
- Onset: 6-10 years old
- Involves physical, emotional and psychological changes
Trends in Puberty

- Consistent decline in age at puberty
- African American have the lowest age at entry into puberty
- Mexican Americans have the fastest decline

Early Life Exposure and Pubertal Development

- Early life factors
  - In utero environment
  - Breast feeding
  - Infancy and childhood nutrition
  - Obesity

- Maternal factors
  - Mother’s age at menarche

- Stress and other psychosocial factors
  - Father’s absence
  - Family conflict/cohesion
Birth-weight-for-gestational age and puberty

Objectives

- To assess the role of birth-weight-for-gestational age and Tanner stage
  - Hypothesis: Compared to girls who are pubertal for breast and pubic hair development, those who are not pubertal will have a greater odds of having being born SGA.

- Evaluate maternal preeclampsia as an effect measure modifier.
Overall study design and population

- Follow-up of a population-based nested case control study
  - 13,000 consecutive deliveries (1993-95) to Norwegian mothers at one hospital
  - 619 normotensive (NT) mother-offspring pairs matched to 307 preeclamptic (PE)
  - Followed at 10.8 and 11.8 years for girls and boys, respectively
Phases of data collection

- Original birth cohort
- Data abstraction of growth intervals
- Follow-up of original cohort in adolescence
Data Collection

Birth weight for gestational age and puberty

Original Cohort 13,000

Mother-Daughter pairs N=282

@ 10.8 years

NT Mother-Daughter pairs N=190
PE Mother-Daughter Pairs N=92

Mother-Son Pairs N=209

@ 11.8 years

NT Mother-Son Pairs N=130
PE Mother-Son Pairs N=78

Non-responders
Birth-weight-for-gestational age and puberty
Measurement of exposure

- Standard population of healthy pregnant Swedish women
- Categorized
  - Small for gestational age (SGA)
  - Average for gestational age (AGA)
  - Large for gestational age (LGA)
Birth-weight-for-gestational age and puberty
Measurement of endpoints

- Girls
  - Breast or pubic hair

- 5 Tanner Stages
  - Categories
    - Stage 1: pre-pubertal
    - Stage 2+: pubertal
Birth-weight-for-gestational age and puberty
Measurement of covariates

- Preeclampsia
  - Causes
  - Diagnosis
    - Around 20 weeks of gestation
    - Diastolic BP to 90mm Hg
    - Proteinuria
  - Severity
Birth-weight-for-gestational age and puberty
Statistical Analysis

- Means and standard deviation
- Frequency distribution
- Stratified analysis
  - Effect measure modification
- Potential confounders
  - Parity, smoking, home ownership, maternal pre-pregnancy BMI
- Univariate and multivariable logistic regression analysis
## Perinatal and maternal characteristics of mother-daughter dyads

<table>
<thead>
<tr>
<th>Variables</th>
<th>NT mother-daughter n=190</th>
<th>PE mother-daughters n=92</th>
<th>Pvalue</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birthweight, grams</td>
<td>3509(480)</td>
<td>2969(834)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Birth length, cm</td>
<td>49.46(1.97)</td>
<td>46.82(6.40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gestational age, weeks</td>
<td>39.70(1.51)</td>
<td>37.32(3.36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pre-pregnancy BMI,</td>
<td>23.29(3.70)</td>
<td>24.57(3.85)</td>
<td>0.010</td>
</tr>
<tr>
<td>Maternal age at pregnancy</td>
<td>28.79(5.37)</td>
<td>27.45(4.80)</td>
<td>0.042</td>
</tr>
<tr>
<td><strong>N (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGA</td>
<td>6(3.19)</td>
<td>9(9.78)</td>
<td>0.010</td>
</tr>
<tr>
<td>Preterm</td>
<td>6(5.56)</td>
<td>12(37.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous preeclampsia</td>
<td>6(5.56)</td>
<td>12(37.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Primaparous</td>
<td>73(40.33)</td>
<td>60(65.22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>42(24.00)</td>
<td>14(15.73)</td>
<td>.246</td>
</tr>
</tbody>
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Birth-weight-for-gestational age and puberty

Proportion of girls who are pubertal for breast or pubic hair at 10.8 years by maternal preeclampsia status

<table>
<thead>
<tr>
<th>Girls: B2+</th>
<th>Girls: PH2+</th>
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<tbody>
<tr>
<td>Normotensive</td>
<td>59%</td>
</tr>
<tr>
<td>Normotensive</td>
<td>57%</td>
</tr>
<tr>
<td>Preeclamptic</td>
<td>26%</td>
</tr>
<tr>
<td>Preeclamptic</td>
<td>29%</td>
</tr>
</tbody>
</table>

*Pubertal parameters*

- **Normotensive**
- **Preeclamptic**
Odds ratios and 95% confidence intervals for birthweight for gestational age and pubertal stage in girls, aged 10.8 years

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<thead>
<tr>
<th></th>
<th>Preeclampsia-adjusted OR§</th>
<th>Fully-adjusted OR €</th>
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<tr>
<td></td>
<td>B1 vs. B2+</td>
<td>PH1 vs. PH2+</td>
</tr>
<tr>
<td>SGA</td>
<td>1.50 (0.49-4.55)</td>
<td>2.87 (0.96-8.55)</td>
</tr>
<tr>
<td>AGA/LGA</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
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</table>

§ Each model is adjusted for maternal preeclampsia status

€ Each model is adjusted for maternal pre-pregnancy body mass index, preeclampsia, parity and smoking during pregnancy.
Summary points

OR for the association for SGA/Puberty

Pubertal vs. prepubertal
Breast/Pubic Hair

SGA vs. AGA/LGA
Mechanism and plausibility of SGA and puberty

- Breast/Genital development
  - Hypothalamic pituitary gonadal (HPG) axis
  - Programming mechanism unknown

- Pubic hair
  - Hypothalamic pituitary adrenal (HPA) axis
  - Under-nutrition HPA axis
Summary of the Evidence

- Strong epidemiological evidence
- Biologic plausibility
- Common exposures with multiple adverse outcomes
- Interdisciplinary approach
Opportunities for Early Life Intervention

- Pregnancy
  - Screening/treatment
  - Education, nutritional modification
- Postnatal/neonatal
  - Maternal diet, Breastfeeding
- Childhood/Adolescent
  - Diet, physical activity
- Overall---strong policies
DON'T FORGET, YOU ARE WHAT YOU EAT.

I NEED TO EAT A SKINNY PERSON.
Acknowledgements

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