The science behind fetal programming: Mechanisms through which early nutrition influences later health outcomes

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Presentation Objectives

- History and underlying mechanisms: fetal programming
- Trace proposed pathways through which maternal nutrition can potentially affect offspring health from the intrauterine stage to adulthood
- Highlight areas for emphasis or reinforcement in assessing maternal and infant health programs/policies
Fetal Programming

Barker’s Hypothesis: pioneering work done by David Barker and colleagues:

Barker and Osmond: LBW and heart disease and hypertension


Thrifty phenotype hypothesis (Hales and Barker): Poor nutrient supply in utero directs nutrients to vital organs (brain) rather than the pancreas and kidneys.


Also referred to as the fetal origins hypothesis, and more recently: developmental origins of health and disease (DOHaD)

Hypothesized mechanisms

Poor nutritional environment in utero:
1) impairs fetal growth, increasing risk of low birth weight due to intrauterine growth restriction

2) results in physiologic changes and systemic malfunctions that predispose fetus to later health problems

Physiologic changes attributed to developmental plasticity: phenotype changes in response to environmental conditions; more likely to occur in the intrauterine period

Poor maternal nutrition “signals” fetus to shift to nutrient-efficient adaptive mechanisms (i.e. brain sparing).

If the change is permanent (prolonged exposure to nutrient deprivation); then the fetus is “programmed” to continue these adaptive mechanisms, allowing the fetus to thrive long-term in a nutrient-deprived environment.
Underlying hypotheses

The problem occurs when the nutrient environment changes from deprivation to abundance.

Individuals born LBW, who were physiologically programmed for scarcity in utero, are hypothesized to have difficulty handling the excess calories/nutrients and are at greater risk of chronic poor health.

Nutrient environment mismatch: more strongly observed in countries undergoing nutrition and socio-economic transitions along with urbanization (shifts in diet and physical activity)

Developmental origins of CVD:
Hypertension

Poor nutritional environment in utero:

- Likely to develop fewer nephrons (brain growth prioritized over kidney growth)
- Weak arterial lining; fewer and narrower blood vessels (as a result of smaller placental size)

Postnatal Implications:

- Fewer nephrons: increased blood processing work load for each nephron; increased wear and tear leading to nephron loss, which further increases blood pressure
- Poor vascular system: require greater pressure to circulate blood. Increased blood pressure not manifested until later in life.

Diabetes

Poor nutritional environment in utero:

- Fewer pancreatic β-cells developed (brain sparing)
- Programmed insulin resistance to retain glucose in the blood and increase supply of energy to the brain (rather than glucose being taken up by tissues and muscles).

Postnatal Implications:

- Impaired insulin secretion, sustained insulin resistance throughout adulthood
Tracing the pathways: linking maternal nutrition to later health outcomes

Cebu Longitudinal Health and Nutrition Survey (CLHNS)

Birth cohort study in Metro Cebu: ongoing prospective study of infants born between May 1983 and April 1984;

Baseline and follow-up surveys: recruited 3327 mothers in their last trimester of pregnancy, followed up from birth through 24 months postpartum; through childhood, adolescence and adulthood.

Maternal nutrition and Infant size at birth

Maternal height and fat reserves in last trimester of pregnancy positively associated with infant size at birth

- 12% LBW (≤ 2500 gms)
- Arm fat area positively associated with newborn weight and length
- Low fat reserves increased risk of proportionate* LBW
- Proportional LBW infants had the shortest mothers

* Lighter and shorter at birth based on Rohrer’s index: (weight x100)/length^2

Among adolescents, pathway to risk of LBW: through poor maternal nutrition

**Underlying**

YOUNG MATERNAL AGE

SES, exogenous community vars

Biological (height)

**Intermediate**

(Nearest)

Nutritional status:

Wt-for-ht at pregnancy

Arm fat area

**Outcomes**

Health at birth

(birth weight and gestational age)


Maternal nutrition

infant size at birth

CVD risk in later life
As offsprings reached adolescence: maternal nutrition at pregnancy attenuated but did not eliminate BW-SBP relationship

- Systolic BP in 16-year old boys inversely associated with:
  - Birth weight
  - Maternal height
  - Maternal triceps skinfold thickness
  - Maternal diet: % energy from protein

- Diastolic BP in 15-year old girls inversely associated with:
  - Birth length
  - Maternal diet: % energy from fat


Dietary fat intakes of CLHNS cohort increased with age and over time at all income levels
Periods of greatest weight gain correspond with periods of most rapid change in income, wealth and urbanization

Mismatch: Being relatively thin at birth (poor prenatal environment), but relatively heavy in young adulthood (better nutrition later in life) is associated with higher systolic blood pressure in young adult Filipinos
Birth weight and weight gain in first 24 months associated with BP*

- Adjusting for adult BMI: inverse relationship between birth weight and systolic and diastolic blood pressure, and odds of pre-hypertension
- Higher weight gain in early life associated with higher BP and risk of pre-hypertension
- But for those with the same adult BMI, weight gain was not associated with BP
- Importance of timing of weight gain: weight gain in first 12 months associated with lean body mass
  In later childhood through adolescence: associated more with adiposity

* COHORTS group: pooled analysis of birth cohort data from Cebu Brazil, South Africa, India, Guatemala

Matrilineal effects on fetal growth: CLHNS intergenerational study

Mother's birth weight have greater effect on offspring birth weight than father's birth weight

- Reported birth weight data of birth cohort participants' children (n=1101) born to 382 FEMALES and spouses of 275 MALE participants
- Models adjusted for mother's age, primiparity, gestational age, infant sex, maternal work status and prenatal care
- 1 kg change in maternal BW predicted a mean increase of 271 g in offspring BW (for paternal BW: mean increase 132g)
- Limitations: reported BW, paternity of MALE ICs not established
- Significance: supports matrilineal contributions to fetal growth

Kuzawa CW and Eisenberg DTA. Intergenerational predictors of birth weight in the Philippines: Correlations with mother’s and father’s birth weight and test of maternal constraint. In press; PloS ONE
Summary

Future directions for DOHaD research:

- More human studies (e.g. maternal salt intake and salt sensitivity of offsprings)
- Maternal stress and offspring health
- Genetics and epigenetic studies

Key messages

- Maternal nutrition at pregnancy influences fetal growth, which subsequently affects health in adulthood
- Importance of programs promoting good health and nutritional status before and during pregnancy (particularly among adolescent mothers)
- Significance of reducing incidence of low birth weight
- Continued monitoring of LBW infants through adulthood (given consequences of later weight gain on BP)
- Role of proper infant feeding in DOHaD
Thank you!