Fetal Origins of Adult Disease

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Objectives

- Participants will be able to
  - Identify 3 chronic disorders that are affected by maternal nutrition/malnutrition
  - Describe 2 measures for consideration by dietitians working in maternal-child health
  - Identify additional areas of research that are needed
Epigenetics

- Epigenetics explains how a stable genome is influenced to be expressed
  - Genes are upregulated or downregulated without changes to genetic sequence
    - Changes to the phenotype results!
    - Changes reset fetal homeostatic set points by changes in metabolism, hormone production, hormone sensitivity, or organ development.
    - Remain with the genome through the child’s life

- Millar and Dean, 2012
Managing Genome-Diet Interactions (Stover and Caudil, 2008)

Nutrient-genome interactions.

Nutrient Absorption
Nutrient Utilization
Food/Nutrient Tolerance
Nutrient Requirement

Genetic Variation

Genome Evolution/Selection
Genome Mutation Rate
In-utero Genome Viability
Genome Programming
Gene Expression

Nutrigenetics

Food/Nutrient

Nutrigenomics
Genetic and Epigenetic Contributions to Health

(Stover and Caudil 2008)

Early Nutrition Experiences
- Malnutrition
- Sub-optimal-nutrient Environments

Risk Phenotype
- Obesity
- Hypertension
- Insulin Resistance

Adult Onset Disease
- Cardiovascular Disease
- Diabetes
- Metabolic Syndrome

“Program”
“Imprint”
Single Nucleotide Polymorphisms (SNPs) and Diet

- One of the underlying mechanisms for metabolic individuality is genetic variation.

  - **SNPs** in genes of metabolic pathways can create metabolic inefficiencies that alter the dietary requirement for, and responses to, nutrients.

  - For example: in adults, SNPs determine whether people develop fatty liver, liver damage and muscle damage when eating diets low in choline (Zeisel et al, 2012.)
Folate-mediated one-carbon metabolism is a conduit between the cellular nutrient environment and genome synthesis and methylation.

ATP = Adenosine Triphosphate
ADP = Adenosine Diphosphate
NADP⁺ = Nicotinamide adenine dinucleotide phosphate
NADPH = Reduced form of NADP⁺
DNA = Deoxyribonucleic acid
DNA Methylation Changes

- While in utero, environmental factors influence the DNA methylation profile at birth

- **Exposure to smoking** leads to DNA methylation change in the aryl hydrocarbon receptor repressor (AHRR) gene in blood; hypomethylation of AHRR occurs

- Novakovic et al, 2014
Placental Dysfunction

Placental dysfunction underlies common and serious pregnancy complications such as fetal growth restriction (FGR), pre-eclampsia, pre-term birth and pregnancy loss.

- The origins of placental dysfunction arise after the first trimester

- Leeuwerke M et al, 2016
Placenta as Regulator

- The placenta: important regulator of the intrauterine environment that links maternal and fetal nervous systems.
  - Placental epigenetic signatures have been associated with neurodevelopment of newborns
    - Quantified through the NICU Network Neurobehavioral Scales (NNNS).
  - Associations have been observed for DNA methylation of genes involved in cortisol ($NR_3C1$, $HSD11B$), serotonin ($HTR_2A$), and metabolic ($LEP$) pathways.
    - Brain epigenetic marks have been involved in idiopathic neurodevelopmental disorders, including Autism Spectrum Disorders (ASD)

- Lesseur et al, 2014
Fetal origins of adult disease (FOAD) from LBW

Dr. David Barker (1938-2013)
Malnutrition in Fetal Period

- Fetal malnutrition induces a nature of thrift in fetuses
  - Higher chance of developing non-communicable diseases, such as obesity and diabetes, if they grow up in the current well-fed society.
  - Similarly, mental stress during the neonatal period can alter the epigenetic expression status of neuronal genes in neonates. Moreover, such environmental, stress-induced, epigenetic changes are transmitted to the next generation via an acquired epigenetic status in sperm.

- The advantage of epigenetic modifications over changes in genetic sequences is their potential reversibility; thus, epigenetic alterations are potentially reversed with gene expression.

- Kubota et al, 2015
Developmental Origins of Health and Disease (DOHaD)

- Fetal over-nutrition and undernutrition: long-lasting effects on neuroendocrine control systems, energy homeostasis, and metabolism

- Sensitive time windows during early development:
  - Environmental cues can program persistent epigenetic modifications
    - Dutch famine birth cohort
    - Fetal overnutrition (exposure to maternal obesity or high blood sugars) -- 10-20% of pregnancies.
    - Epigenetic changes: predispose the offspring to develop metabolic disease and transmit the adverse environmental exposure to the next generation.

  - El Hajj N et al., 2014
DOHaD

- Early exposures to threat or adverse conditions have lifelong consequences.
- The *maternal endocrine 'fight or flight' system* is a source of programming information for the human fetus to detect threats and adjust their developmental trajectory for survival.
- Fetal exposures to intrauterine conditions including *elevated stress hormones* increase the risk for a spectrum of health outcomes depending on the *timing of exposure*, the *timetable of organogenesis* and the *developmental milestones* assessed.
- Fetal exposures to biological markers of adversity have significant and largely negative consequences for fetal, infant and child emotional and cognitive regulation and *reduced volume in specific brain structures*.

— Sandman and Davis, 2012
Inter-Individual Variations

DOHaD hypothesis: supported by a large number of direct animal studies and a smaller number of compelling observational studies in humans

- Little direct evidence exists in humans
  - Epigenetic variation should be apparent in a tissue relevant to the disease of interest prior to phenotypic onset in order to avoid confounding and the potential for reverse causation.
- The functional relevance of specific epigenetic change must be demonstrated.

“Only large longitudinal life-course studies commencing prior to birth, with extensive environmental exposure data and biospecimens, can provide direct evidence in support of a role of epigenetic processes as drivers of the DOHaD in humans.” (Saffery, 2014)
Paradigm

Environmental stressors:
- a variety of environmental and occupational hazards
- deficiency and oversupply of nutrients and energy

• Grandjean et al, 2015
OBESITY

More than just Overnutrition
Global Obesity and Metabolic Disease

- The generally accepted cause of obesity is overconsumption of calorie-dense food and diminished physical activity (the “calories in-calories out” model).
  - Emerging evidence: environmental factors can predispose exposed individuals to gain weight, irrespective of diet and exercise.

**Environmental obesogen model:**
- chemical exposure during critical stages in development can influence subsequent adipogenesis, lipid balance and obesity.
- some obesogens elicit transgenerational effects on a variety of health endpoints

*Janesick et al, 2014*
Endocrine Disrupting Chemicals (EDCs)

- Obesogenic EDCs may inappropriately stimulate adipogenesis and fat storage, influence metabolism and energy balance, and increase susceptibility to obesity.
  - Tributyltin, brominated diphenyl ether 47, and polycyclic aromatic hydrocarbons alter methylation of peroxisome proliferator-activated receptor-γ (PPARγ) -- the master regulator of adipogenesis, or its target genes.
  - Advances in epigenomics:
    - potential epigenetic markers for obesity that can be detected at birth
    - basis to determine the effects of developmental exposure to obesogenic EDCs in humans.
    - important to monitor low-level early-life environmental exposures

Birnbaum and Miller, 2015
Stel and Legler, 2015
PPARγ (Ahmadian et al, 2013)
Double Burden of Disease

Undernutrition and Overnutrition
Double Burden of Disease

**Undernutrition**
- Stunting, wasting, infectious diseases

**Overweight and Obesity**
- Non-Communicable Disease (NCD): risk more with lifestyle changes and urbanization

Social and environmental factors such as parental migration, financial situation of the household, child-rearing knowledge and practices of the primary caregivers

Prominent in Sub-Saharan Africa, Asia (rural China, India)

Feng et al, 2015
Maternal and Child Malnutrition

Child malnutrition in low-income and middle-income countries encompasses both undernutrition and a growing problem with overweight and obesity.

- Prevalence of stunting of linear growth of children younger than 5 years has decreased during the past two decades.
  - Higher in south Asia and sub-Saharan Africa.

- Deficiencies of vitamin A and zinc result in deaths.

- Deficiencies of iodine and iron, with stunting, can contribute to children not reaching their developmental potential.

- Undernutrition (including fetal growth restriction, stunting, wasting, and deficiencies of vitamin A and zinc, and suboptimum breastfeeding) causes 3.1 million child deaths annually...45% of all child deaths in 2011 (Black et al, 2013).
Maternal and Child Malnutrition

• Maternal undernutrition contributes to fetal growth restriction, which increases the risk of neonatal deaths and, for survivors, of stunting by 2 years of age.

• Suboptimum breastfeeding results in an increased risk for mortality in the first 2 years of life.
Cardiovascular, Liver, Lung, Renal, Reproductive Changes

The impact of perinatal insults
Perinatal Insults and Cardiovascular Disease

- The cardiovascular, renal and metabolic diseases during adult life that occur as a consequence of several insults during fetal and postnatal periods are secondary to multiple structural and functional changes (Tomat and Salazar, 2014)

- Maternal obesity is a risk factor for the development of cardiovascular diseases in the child later -- an exaggerated leptin surge (Samuelsson et al, 2014)
Perinatal Insults, Hypertension and Renal Changes

- Maternal undernutrition, maternal glucocorticoids, placental insufficiency, and maternal sodium overload can program changes in renal Na(+) excretion leading to hypertension.

  - Fetal exposure to an adverse maternal environment may reduce GFR by decreasing the surface area of the glomerular capillaries.

- Paixao and Alexander, 2013
Lactation and Insulin Resistance

- Both early weaning and overfeeding by more milk intake may lead to insulin resistance in later life.
  - Maternal stress, obesity, hyperglycemia, and even smoking during lactation might also cause reduced insulin sensitivity in the offspring.
  - Breast milk may be the “agent,” transferring altered levels of hormones, insulin, or fatty acid contents from maternal circulation to neonate (Jiang et al., 2013.)
Perinatal Insults and Nonalcoholic Fatty Liver Disease (NAFLD)

- Most common liver disease globally
  - Altered early life nutrition is now associated with an increased risk for the development of NAFLD

Li et al, 2015
Perinatal Insults and Lung Disease

- **Perinatal insults:**
  - Intrauterine growth restriction, preterm birth, maternal exposure to toxins, or dietary deficiencies produce deviations in the epigenome of lung cells
  - Final stages of lung development
  - DNA methylation, histone modifications, and microRNA changes are all observed in various forms of lung disease

- **Joss-Moore et al, 2015**
Perinatal Insults on the Female Reproductive System

- Reproductive maturation and function
  - primordial follicle pool is established early in life
  - insults cause decline in ovarian follicular reserve, changes in ovulation rates, and altered age at onset of puberty
  - protein malnutrition especially a concern

Chan et al, 2015
Diabetes (T2DM)

T2DM – worldwide a problem – 2.8% - 4.4%

India the country with the highest prevalence
Islet Cells

Islets are the most plastic during the early life course; hence programming during fetal and lactational life is most potent.

- High fat exposure (through acute hyperglycemia) during weaning initiates beta cell programming and dysfunction

Cerf, 2015
Type 2 Diabetes Mellitus (T2DM)

- Multifactorial disease: genetic, epigenetic, and environmental factors.
- Maternal factors during pregnancy may increase the risk of diabetes in offspring in later life:
  - malnutrition, hyperglycemia, obesity, behavior (smoking, drinking, and junk food diet), hormone administration, and stress
- In neonates:
  - catch-up growth, fatty acid exposure during lactation, glucocorticoids administration, and stress have all been found to increase the risk of insulin resistance or T2DM
  - unfavorable socioeconomic situation, famine or obesity also increase susceptibility to T2DM in adults.

High Fat Programming during PG/BF

The maternal nutritional condition and fatty acid intake during pregnancy and/or lactation are critical for programming:

The maternal body accumulates fat; in late pregnancy, the lipolytic activity in the maternal adipose tissue is increased.

Fetal exposure to trans fatty acids appears to promote early deleterious effects in the offspring’s health.

Maternal intake of saturated fatty acids seems to trigger alterations in the liver and adipose tissue function associated with insulin resistance and diabetes.

PUFAs (particularly arachidonic acid, EPA and DHA) play an important and beneficial physiologic role in the offspring who receive these fatty acids during critical periods of development.

Mennitti et al, 2015
Protein Insufficiency during Pregnancy

- The effect of low protein diet during pregnancy on postnatal \( \beta \) cells \((\text{Jiang et al, 2013.})\)
  - increased oxidative stress, fibrosis
  - defective mitochondriogenesis, mitochondria dysfunction
  - increased cell differentiation instead of proliferation
Neurological Conditions

The brain is a high risk organ
Stress and the Fetal Brain

Stress During Pregnancy

• Psychobiological markers of stress during pregnancy, especially early in gestation, result in:
  – delayed fetal maturation
  – disrupted emotional regulation
  – impaired cognitive performance during infancy
  – decreased brain volume in areas associated with learning and memory in 6- to 8-year-old children

The Fetal Brain

• During gestation, the fetal brain develops dramatically as structures and connections form, providing the foundation for all future development. The fetal environment plays a critical role in these early neural processes, for better or for worse.

• Exposure to maternal stress can sometimes have deleterious effects on the fetus, depending on the cause, timing, duration, and intensity of stress.
Stress and the Brain  (Buss et al 2012)

Conceptual Framework

Prenatal Perturbations
- Maternal stress
- Maternal nutrition
- Exogenous glucocorticoids
- Exogenous CRH
- Infection/ inflammation
- Prenatal drug exposure

Alterations in the brain
- Size and shape of gray matter structures (e.g. hippocampus, amygdala)
- Cortical thickness
- Functional connectivity
- White matter fiber tracts

Psychopathology/ Developmental Disorders
- Autism
- ADHD
- Schizophrenia
- Affective Disorders
- Dementia
Prenatal Inflammation

- Known risk factor for long term neurobehavioral disorders including cerebral palsy, schizophrenia, and autism
  - Immune response and adverse neurobehavioral outcomes occur in the exposed fetus.
  - The immune system in the placenta is activated, inducing a fetal immune response and subsequent brain injury.
  - Changes in the fetal brain lead to changes in gene expression patterns into the neonatal period.
  - Subclinical intrauterine inflammation can lead to fetal brain injury, mechanistically associated with long term adverse outcomes for exposed offspring.

Elovitz et al, 2011
Maternal Obesity and High-Fat Diet

- Increased obesity and increased vulnerability to mood disorders

- Programming of brain and behavior by perinatal diet is propagated by inflammatory mechanisms--- interleukin [IL]-6 and 11-1β

Bolton and Bilbo, 2014

Sasaki et al, 2013
Cancer

Genes + Environment
Cancer

Tumor cell plasticity - Intrinsic factors govern cell functioning

More, larger and longer studies are needed (Brock et al, 2015)

Non-communicable diseases (NCDs) and maternal health are closely linked. NCDs such as diabetes, obesity and hypertension have a significant adverse impact on maternal health and pregnancy outcomes, and future generations.

The cycle of vulnerability to NCDs is repeated with increasing risk accumulation in subsequent generations. (Kapur, 2015)
Effects and Actions

Interventions
Effects of Nutritional Insults
What is the Time to Intervene?

Development is Most Important Time to Intervene to Prevent Disease

- Timely intervention produces substantial risk reduction
- Impact of adult intervention is small

Life course

Fixed genetic contribution to risk is small

Hanson and Gluckman
First 1000 Days Project

• Issues:
  – Low birthweight – high risk for DM and hypertension later
  – Breastfeeding – exclusive for at least 6 months
  – Stunting – 20% begins in the womb if mom is malnourished
  – Acute Malnutrition – wasting leads to stunted growth, cognitive deficits and NCDs in adulthood
  – Anemia – diminished energy and health in women and their children
  – Obesity – childhood obesity contributes to diabetes and hypertension

http://thousanddays.org/
First 1000 Days Principles

• The nutritional health of women and children, particularly during the 1,000 day window between pregnancy and age two, is a policy and funding priority.

• The world’s mothers and future mothers are valued, healthy and well-nourished.

• More babies are exclusively breastfed from birth to six months and are continuing to breastfeed for at least one year.

• Women are empowered and supported to breastfeed and make choices about how to nourish their children in a way that is free from predatory marketing and commercial influence.

• Women and young children eat a healthy and diverse diet of nutritious foods. This requires a shift in food and agriculture policies, food systems and environments and social norms so that healthy foods are available, affordable and desired.

• Women and children have access to quality health care, clean water and sanitation, and social support systems.

• Life-saving treatment for acute malnutrition reaches those who need it the most.

• There is greater collaboration to bring an end to malnutrition in all its forms.
Public Health Measures

- Coexistence of stunting, overweight or obesity, and anemia at the national, household calls for policies and programs to prevent these conditions

- Educate the public, especially young women

- Evaluate nutrient requirements on a regular basis
Possible genomic criteria for establishing dietary requirements.

EAR = Estimated Average Requirement;
UL = Tolerable Upper Intake Levels
RDA = Recommended Dietary Allowances
DNA = Deoxyribonucleic Acid
Our Goals

Promote Maternal and Child Health Strategies

• Promote health literacy in the public

Reduce Infant Malnutrition

• Provide high-quality complementary foods
• Promote well-balanced dietary patterns
What Can We Do?

• Promote **preconceptual care** to modify a woman’s medical, behavioral and social risks through interventions.

• Diagnose and treat NCDs to reduce their impact during pregnancy:
  – Give ample time to treat hypertension, diabetes, obesity, systemic lupus erythematosus, thyroid disease, anemia, epilepsy, asthma, and cardiac disease.
  – Manage these conditions carefully during pregnancy to prevent long-term consequences for mother, child, and future generations.

• Hadar et al, 2015
Future Research Considerations

• Sample size
• Potentially confounding factors
• Tissue heterogeneity
• Reverse causation
• The role of genetics in modulating epigenetic profiles

– Januar et al 2015
Let’s NOT Be Too Late....
References


References


References


Leeuwerke M et al. DNA Methylation and Expression Patterns of Selected Genes in First-Trimester Placental Tissue from Pregnancies with Small-for-Gestational-Age Infants at Birth. Biol Reprod. 94:37, 2016.


References

Paixao AD, Alexander BT. How the kidney is impacted by the perinatal maternal environment to develop hypertension. Biol Reprod. 89:144, 2013.

Saffery R. Epigenetic change as the major mediator of fetal programming in humans: Are we there yet? Ann Nutr Metab. 64:203, 2014.


