Maternal Nutrition & Placental Function

Prof. Dr. İskender BAŞER
GATA Kadın Doğum Anabilim Dalı (E)
Ankara
Human Placenta
Discoid Deciduate Haemochorial Chorioallantoic

1. Exchange »
   gas
   nutrients & waste products

2. Hormonal »

3. Regulation & Modulation »
   nutrients
   thermoregulation
   genes

4. Immune » ............ Intrauterine Programming

Prof. I Başer
Recent and rapid worldwide increase in non-comunicable disease challenges the assumption that Genetic Factors are the primary contributors to such escalation of adult health problems.

This revisited paradigm states environmental factors during preperi-conception, gestation, and lactation shape individual and predisposition for DOHaD.

Sexual Dimorphism is also a major determinant for DOHaD.

McAllister, 2009
Barker 1990
Nutrients

- **Macro**
  - Carbohydrates, Protein, Lipids

- **Micro**
  - Iron, iodine, selenium, zinc, folate, other vits & factors

Terminology

- **Under Nutrition (MUN)**
  - starvation

- **Over Nutrition (MON)**

**Mal Nutrition (MMN)**
Placenta Fetal development
Abnormal Nutrient availability

1. High intake

2. Low intake
   - Famine, lifestyle, nausea-vomiting

3. Short interpregnancy interval
   - Nutritional depletion

4. Teenage pregnancy
   - Compete food with own fetus
     - ↓ birthweight X2
     - ↑ preterm delivery X3
     - ↑ neonatal mortality X3
     - King 2003
Human placenta Synsitium Nutritional Sensing System

1. Adenosine monophosphate – proteinkinase
   - Global energy
2. Glucogen Synthase3
   - glucose sensor
3. Hexoe Amino signal Pathway
   - glucose, glutamine, acetyl-CoA
4. AA response signal transduction Pathway
   - Ess.AA
5. mTOR (mechanistic Target of Rapamycin) Complex
   - integrates nutrient and growth factor signaling
Placental Transfer
Romero R et al 2017
Optimal maternal nutritive supply during pregnancy
Critical role for placental & fetal unit

- Pre Peri Conceptional
- During pregnancy
  - Early
  - Late

- Various consequences According to Fetal Sex
in Utero Fetal Programming

- Epigenetic
  - Genomic imprinting

- Sexual Dimorphism
Epigenetic

• Impact Life has on the function of Genes
• 1940 Conrad Waddington
• Interactions between Environment and Genes
  ▪ Gene activity changes
  ▪ Structure of DNA stable
    • Chemical Mechanisms
      o Methylation
      o Histone Post translation Modifications
• 1962 Joel Wallach
  ▪ Many disease thought genetic transmission infact nutritional deficiency
  ▪ Ricets, scurvy, beriberi  lacagnia 2018
Epigenetic Mechanism

- Key molecular mechanism underlying developmental programming of Fetal Phenotype
- Heritable gene expression changes without change in DNA structure

- DNA Methylation (CpG)
  - Covalent modification of chromatin
  - Non-coding RNA

- Histone Proteins Acetylation

- Memory of Cell Identity
Epigenetic Mechanism

- Nutrition, micronutrients, Energy metabolism, external Toxins, Stress, …..

- Gametogenesis
- Placenta & Conceptus development

- Cell identity Changes
Genomic imprinting

- Epigenetic mechanism
- **Parent of Origin Gene Expression**
- **Nutrition linked Transgenerational Effect** on Development and Growth
Sexual Dimorphism
Tarrade 2015

- **MMN**, mat stress etc. Environmental Factors Affect Males and Females in a Different way
  - Bale2011, Aiken2013

- Dimorphism may appear very early during development (Blastocyst) Benenjo 2010

- Rate of cell division Faster in XY Mittowitch 1993

- **Maternal Starvation / Pl Size & Area** ↓

- More severe for xy Rosenboom 2011

- **Adult Hypertension** Abeleen 2011

- **Metabolic syndrome** More prevalent for xy Owens2007

Prof I Başer
High Fructose intake… **Obesity**

**PI W ↓ Only in males**

Oleic acid

↓in XY , ↑ in XX

Some Genes Set For Gender of The Fetus

X (10 / 34), Y (3 /7), Autosomes (immun regulation)

**Female Placenta more adaptive deleterious environment than Males** Cox 2013
Maternal Mal nutrition (MMN) Placenta (Pl)

1. Weight

• Fetal consequences
  2. Histomorphology
    1. Development & Growth
    3. Vasculogenesis &
    2. Hormone modulation & secretion
      Angiogenesis
    3. Epigenetic Influences
    4. Nutrient transfer Capacity

4. Long term Programming on

Progeny
Hunger kills more people each year than AIDS, malaria and tuberculosis combined. About **21,000 people die of hunger** or related causes **every day**.

Prof İ Başer
• Global MUN (avg 400 cal/d), Starvation

• **3rd trimester**
  - Pl W ↓ Birth W ↓ Pl W/ BW Ratio **Unaltered**

• **Only 1st Trimester**
  - Pl W ↑ Birth W **Normal** Pl W/ BW Ratio ↑ **Altered**

• Placental Adaptation in Early Pregnancy

• Sheep model Similar Observations  
  
  Heasman, 1998
Selective Protein Deprivation
A Key Factor
Rat Model  Langley-Evans, 1996

9 – 18 % ↓

• During Pregnancy
• PI W↑ Fetal Growth ↓

• Early Pregnancy

• PI W ↑ Fetal Growth →↑
Placental Histomorphology
Human Observations and
Animal Models

• Global MUN IUGR fetuses
• Surface area (Exchange Villi)
• Barier Thickness
• Cell Composition
  - sibley 1997, aherne 1966

• Trophoblast Apoptosis ↑↑
• Surface Area 70% ↓
• Barier Thickness 40 % ↑
• Placental Migration to Advantageous Area

Prof. I Başer  • Balkacemi 2009, Roberts 2001
Human placenta

Synsitium

Nutritional Sensing System

- Adenosine monophosphate – proteinkinase
  - Global energy
- Glucogen Synthase3
  - glucose senser
- Hexoe Amino signal Pathway
  - glucose, glutamine, acetyl-CoA
- AA response signal transduction Pathway
  - Ess.AA
- mTOR (mechanistic Target of Rapamycin ) Complex
  - integrates nutrient and growth factor signaling

- Maternal starvation… impair placentation….IUGR
- Placental-Fetal Unit Adaptive Mechanism and Response

- Disordered Nutritional sensing system
  - Jansson 2013, Roos 2009, Rosario 2013
• Animal Model Ewes
• Placental Vascularity↑
• VEGF receptor expression↓
• Nutrient transfer↓
  ▪ Redmer 2004

• IUGR Human Pl
• NO↓NO syntethase ↓
• Vascular resistance↑↑
Nutrient Transfer Capacity
Glucose

• Rat Model, Global MUN
• Maternal Glucose↓…. Fetal Glucose↓↓
• Glucose Transporter 3 ↓
  • Lesage 2002 ↓

• Global MUN Affects placental Transport Mechanism
Nutrient Transfer Capacity Fatty Acids (FA)

- IUGR Placenta
- ↓ Ess.FA → Fetus
  - Magnuss 2009
- ↓ Arachidonic acid
- ↓ Docosa Hexaneoic Acid
- ↓ Linoleic acid

- Altered Microvillous Plasma Membrane Hydrolase Activity
MUN placental Fetal Transport Critical Factors

1. NO ↓ ↓ NUTRIENT TRANSPORT  
   Wu 2004

2. Glucocorticoids ↓ glucose  
   Langdown 2001

3. Imprinted placental gene
   MICE- RATS
   • ↓ PLACENTA IGf2 EXPRESSION
   • ↓ PLACENTAL GROWTH
   • Sibley 2003
MUN
Hormone Secretions & Modulations

- Affects
- Maternal-placental-fetal hormone secretions and appropriate balance
MUN
Hormone Secretions & Modulations

• Glucocorticoids
  ▪ Excessive exposure to Endogenous **Corticoids**
  ▪ ↓ fetal growth…. **Anxiety Disorder** in Later Life
  ▪ **Disturbed hypothalamo-pituitary-adrenal axis** in Newborn
    • ↑ basal corticosteron
    • **Cognitive defects**
      • Wellberg 2000, Levitt 1996
MUN
Hormone Secretions & Modulations

- Insulin Like Growth Factor (IGF)
- Periconceptional & Pregnancy Animal Model (sheep)
- Fetal insulin
- IGF1
- IGFBP3

Fetal Growth
Altered Fetal Programming

Leptin (Adipocin) (Satiety Factor)

- IUGR ↓ Leptin
- Apetite Stimulation Pathway (NPY mRNA expression)
- Supressed Anorexigenic pathway
- Obesity in Adult Life
Transgenerational Inheritance

- ↓↓ Diet Rat
- SGA newborn

- Diabetes
- Males fathered
  - Diabetes among Progeny
  - Lacagnia 2018
Maternal Overnutrition
Obesity and Placenta

- BMI ≥ 30 kg/m², prevalence increasing
- Dyslipidemia, hyperleptinemia, hyperinsulinemia, exaggerated systemic inflammation
- Macrosomia or IUGR, stillbirth, GDM, Preeclampsia, ↑ fetal anomaly rate, ↑ CS rate,
- Adult Life
  - Obesity
  - Diabetes

Prof I Başer
Obesity
Placental Weight

• # 37482 obes Pregnant Wallace 2012

• ↑BMI ↑ PI W ↑ BW ↓ PI Functions

• ↑LBW mc Donald 2010

• No Effect on BW but ↓ PI Functions Dube 2012

Obesity
Placental HistoMorphology

• Synsitio Capiller mambran thickness ↑ Roberts 2011

• ↑ lipid Droplets (Rabbits) Tarrade 2013

Prof I Başer
**Obesity**

**Placental Vascular Functions**

- Disordered Endothelium & Smooth Muscle (Preeclampsia) (Stewart 2007)

**Obesity**

**Placental nutrient Transfer**

- Altered lipid transfer (Child Obesity) (Dube 2012)
- ↑ Glucose & Amino Acid Transfer
- ↑ Signaling Pathways (IGF, mTOR) (Jansonn 2013)
Obesity
Placental Inflammation

- Well correlated Systemic Inflammation
- ↑ Excessive nutrient transport Jones 2009
MUN& Low Birth Weight intrauterine programming

- Insulin resistance
- Type2 diabetes
- Hypertension
- Physical, mental impairments
- Delayed cognitive functions
- ↑ Adiposity, Obesity
- Maldeveloped skeletal muscle mass
- Liver developmental and functional disorders

Helsinki Birth Cohort
Barker et al 2005 NEJM
Trajectories of Growth among children who have **coronary events** as adults.
# 20431 case

**Fig. 3.** Variations in the normal processes of development and later chronic disease.
Thank You
Conclusions

- Optimum Maternal Nutrition well before pregnancy
- Balanced diet
- Both UnderNutrition and OverNutrition Hazardous for Placental Functions
- First trimester stress is very important
- Besides immediate Perinatal Outcome
- Long term consequences must take in to account