**Disclosure to Participants**

Notice of Requirements For Successful Completion

Please refer to learning goals and objectives

Learners must attend the full activity and complete the evaluation in order to claim continuing education credit/hours

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Charles A. Ducsay, M.S, Ph.D.- No COI/Financial Relationship to disclose

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**Outline**

1) Develop the concept of fetal/developmental programming of adult disease: The Barker or Thrifty Phenotype Hypothesis

2) Survey the impact on adult health with a focus on diabetes and obesity

3) Explore the potential basic science models and clinical correlates of fetal programming of:
   a) β-cell function
   b) adipose tissue function

4) Discuss new therapeutic developments/future directions and impact

5) Summary/Conclusions

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"When a variation is of the slightest use to a being, we cannot tell how much of it to attribute to the accumulative action of natural selection, and how much to the conditions of life."

Charles Darwin (1859)

"Human epidemiological studies show that cell/organ structure, metabolism, and physiology are permanently altered during development by fetal nutrient deprivation." Barker Hypothesis (1989)
What happens here can influence health here.

Fetal Growth Trajectory Is Correlated to Impaired Glucose Homeostasis in Adulthood

- Birthweight
- Risk of Gestational Age
- Small for Gestational Age
- Macrosomic
- IUGR accounts for 4-7% of all births in developed countries.
- IUGR accounts for a high percentage of neonatal morbidity and mortality.

The prevalence of impaired glucose tolerance (IGT) in adulthood fell from 27% (<2.5 kg BW) to 6% (>3.4 kg BW).

The Thrifty Phenotype Hypothesis

- Adaptations including smaller size and decreased metabolic activity, help the fetus to develop in an environment where nutrient availability is limited or reduced.
- The Thrifty Phenotype fetus has received a maternal “forecast” for a tough nutrient road ahead. Essentially selection of an appropriate growth trajectory in response to the nutrient environment.
- However, after birth, if nutrients are again plentiful, the “catch up” growth further enhances the likelihood of metabolic disorders.

Dutch Famine Studies


"Unintended Consequences"
Long-term Consequences of Exposure to Famine According to Time of Gestation

<table>
<thead>
<tr>
<th>Timing of Exposure During Gestation</th>
<th>In EARLY gestation</th>
<th>In MId Gestation</th>
<th>In LATE gestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose Intolerance</td>
<td>Glucose Intolerance</td>
<td>Glucose Intolerance</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>Obstructive Airway Disease</td>
<td></td>
<td></td>
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<tr>
<td>Coronary Heart Disease</td>
<td>Microalbuminuria</td>
<td></td>
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<tr>
<td>Stress Sensitivity</td>
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</table>

Timing of Exposure During Gestation

Placental restriction (PR) of growth before birth in rats and sheep causes similar changes in insulin secretion and sensitivity with ageing as IUGR humans. This includes decreased insulin sensitivity and impaired insulin secretion.

Why do we use the sheep as a model?

- Fetus similar in size and developmental stages to human
- Similar cardiovascular and endocrine systems
- The only fetal model for studying normal (or regulated) in vivo metabolism under normal (or regulated) non-stressed, unanaesthetized conditions.
- These conditions allow surgical placement of catheters for recovery and later study.

IUGR and Insulin Action in Humans

Restriction of growth before birth enhances insulin sensitivity in neonates with reversal to impaired insulin sensitivity by adulthood. Insulin secretion is impaired from early postnatal life, and together these contribute to increased risk of T2D in the adult who was small at birth.
Insulin is an important anabolic hormone in the fetus

- Alteration in β-cell development and function in utero may augment fetal growth restriction and lead to aberrant glucose metabolism and/or β-cell dysfunction in adulthood.

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Conclusions For IUGR in Fetal Development in the Sheep Model

- IUGR resulting from placental insufficiency decreases β-cell responsiveness.
- IUGR fetuses have a lower insulin mRNA concentration resulting in less insulin content.
- β-cell area and mass is reduced in PI-IUGR fetuses.

IUGR Pancreatic Development / Function

<table>
<thead>
<tr>
<th></th>
<th>Human IUGR</th>
<th>Rodent IUGR</th>
<th>Sheep IUGR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal Glucose</td>
<td>26%</td>
<td>37%</td>
<td>33%</td>
</tr>
<tr>
<td>Fetal Insulin</td>
<td>50%</td>
<td>51%</td>
<td>59%</td>
</tr>
<tr>
<td>Pancreatic Insulin Content</td>
<td>33%</td>
<td>36%</td>
<td></td>
</tr>
<tr>
<td>Morphology (mass)</td>
<td>34%</td>
<td>34%</td>
<td>18%</td>
</tr>
<tr>
<td>β-cell Responsiveness</td>
<td>89%</td>
<td>39%</td>
<td>55%</td>
</tr>
</tbody>
</table>

Thrifty Phenotype Hypothesis

Insulin Resistance: β-cell malfunction
But wait, it gets even more scary…

Transgenerational Effects
- A large number of animal studies have shown the effects of undernutrition during fetal/perinatal development on the glucose metabolism of offspring (F1) in adulthood. However, several studies have shown that glucose metabolism is also altered in the offspring (F2) as well as grand offspring (F3) of fetally malnourished F1 females, even when the F1 and F2 females have been well nourished since weaning.
- In girls that are born small and remain short, uterine size is reduced which in turn would influence fetal growth and reduce weight in their progeny.

Causes of Obesity
- Socioeconomic factors such as changes in lifestyle (e.g. decreased physical activity and high caloric diets) contribute significantly to the increase in obesity. But, these factors provide only a partial explanation of the early obesity epidemic, indicating an underlying non-genetic predisposition to obesity.
- Human growth restriction early in gestation increases the probability of developing obesity in later life, particularly if combined with rapid compensatory growth after birth.

Adipose Tissue Types
- White Adipose Tissue (WAT)
  - major sites of lipid storage and of leptin synthesis and secretion
- Brown Adipose Tissue (BAT)
  - express the mitochondrial uncoupling protein UCP1
  - participates in cold and dietary induced thermogenesis
- Beige/BRITE (brown-in-white)
  - reside in WAT yet exhibit BAT-like characteristics:
    - UCP-1 expression
    - upon stimulation, expend energy via lipolysis and thermogenesis.

The Good, The Bad and The Fatty
- The genetic component of obesity is a minor contributor to the dramatic increase in the observed rate of obesity
- A significant proportion of obese/overweight children are from non-obese, non-diabetic mothers

What gives healthy “brown fat: its darker color? The presence of mitochondria that generate energy for the cells. The “holy grail” is how to leverage the conversion of energy-storing white fat into energy burning, beige fat.
Fetal Perirenal Adipose Tissue (PAT)

- Fetal perirenal adipose tissue is different from adult tissue in that it is neither distinctly white adipose tissue nor brown adipose tissue, but rather has the characteristics of both tissue forms.
- Adipocytes contain an abundance of mitochondria, which is a characteristic feature of the thermogenic brown adipocyte.
- During the neonatal period, there is an expansion of the WAT phenotype as the perirenal adipose tissue (PAT) expands into the abdominal WAT fat mass. Abdominal fat plays a key role in obesity.

LONG TERM HYPOXIA (LTH) MODEL

- Sea level controls
- LTH Maintained at 3,800m from ~day 40 to near term
- In vivo catheterized fetal studies @ ~137-141 days gestation
- In vitro studies: Fetal tissue collected at days 138-141 or postnatal days 12-14

Oxygen is a Another Key “Nutrient”

Long Term Hypoxia (LTH)

- Pregnant women at high altitude (long term hypoxia): incidence of toxemia is elevated
- IUGR persistent fetal circulation neonatal intraventricular hemorrhage
- Women who smoke during pregnancy
- Anemic patients
- Women with heart or lung disease
- Pre-eclampsia

All of these conditions may contribute to prolonged fetal exposure to hypoxic stress - “nutrient” restriction

Leptin

- Protein produced in adipose
- In the adult, acts at the level of the hypothalamus to signal adequacy of nutritional status, thereby regulating energy intake and expenditure, thus weight gain and fat deposition

Hypoxia-inducible gene

- Elevated leptin following hypobaric hypoxia or in patients with sleep apnea

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LTH Enhances Fetal Leptin

- Barcroft Laboratory, White Mountain Research Station

- Leptin
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  - Hypoxia-inducible gene
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- LTH Enhances Fetal Leptin
So how does the magic happen?

**Epigenetics**

Heritable changes in gene expression that are not caused by changes in the primary DNA sequence.
LTH Alters miR and Gene Expression Perirenal Adipose Tissue in the Transition From Fetus to Lamb

RIP140 inhibits BAT/beige

Epigenetic Programming of Obesity
Early life nutritional levels (under- or over-nutrition)  
Epigenetic changes in hypothalamic appetite regulatory genes  
Metabolic disorders such as obesity and diabetes

Leptin Impacts Brain Appetite Pathways that Regulate Food Intake and Activity

† Food intake
‡ Activity

gestational hypoxia

LEPTIN

Ducsay et al., 2015

Effects of Restricted Diet Exposure

Timming of Intervention is Critical

Future Directions

The molecular results of epigenomic studies characterized by alterations in DNA methylation and miRNAs suggest novel therapeutic interventions that may be used in managing the metabolic disturbances observed in diabetes and obesity.

Future Directions

1) Preventing or reducing the initial epigenetic changes by manipulating fetal methyl donor supply (maternal dietary supplementation with methyl donors and cofactors in late pregnancy, (e.g. folate)

2) Restricted placental transport of nutrients results in IUGR, which is associated with fetal programming. Therefore alleviating IUGR by increasing placental nutrient transport could represent an effective way of preventing fetal programming of adult disease. Maternal IGF-1 administration stimulates placental and fetal growth and has been suggested as a possible therapy in cases of IUGR.
Fetal programming involves plasticity, permitting the fetus to respond to environmental impacts by following a developmental path that may be associated with an adaptive advantage.

Any intervention aimed at minimizing the long-term adverse effects of a suboptimal environment may jeopardize any short-term advantages of fetal intrauterine adaptations.

**Future Directions**

Reversing epigenetic changes in early postnatal life, before they become permanent.

- Extensive studies of the underlying mechanisms for impaired insulin action in the IUGR rat and sheep have provided the basis for designing interventions to prevent diabetes after IUGR, with promising results from initial studies of neonatal exendin-4 (Byetta).
- GC-1
- Resveratrol

**GC-1 TRANSFORMS “BAD” FAT TO “GOOD” FAT**

Activation of the thyroid hormone receptors by GC-1 (a synthetic agonist) strongly induces a brown-fat-like program of adaptive thermogenesis and increased metabolism in white adipocytes both in vivo and in vitro.

**Lifecycle Chain of Risk for Programmed Chronic Diseases**

Through a better understanding of these mechanisms, we can improve prediction and prevention of pregnancy complications leading to fetal programming, ultimately improving the health outcomes of mothers and their offspring.

"Art is me, Science is we"

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This work supported by NIH grants P01-HD3126, P01 HD083132 and R01HD051951
“The devil has put a penalty on all things we enjoy in life. Either we suffer in health or we suffer in soul or we get fat.”

Albert Einstein, 1879–1955