Foetal programming and long-term implications for metabolic and endocrine function

Mette Olaf Nielsen

EAAP Tuesday 26 August 2014
Low and high birth weight increase disease risk in adult life

Barker, 1998
Low and high birth weight increase disease risk in adult life

In DK: appr. 25% of babies have birthweights deviating more than 10-15% from the average. Are all at risk? 
**No!!! But some of them!!!**

Is birth weight a reliable marker?  
**No!!! Compensatory growth later in gestation**

After 25yrs of research can we point out the ones at risk?  
**No, not with certainty!!!**

Do we have a cure or a treatment?  
**No, not yet !!!**
Aim of studies

Improve understanding of:

• Mechanisms underlying malnutrition induced fetal programming
• How manifestation of fetal programming is impacted by the postnatal diet

• Biological markers -> ID of programmed individuals early in life
• Intervention strategies (dietary?) -> Reverse/alleviate adverse programming outcomes
Fetal programming: The sheep as experimental model

Advantages:
• Size (50-75 kg)
• Litter size: Singletons and twins (triplets)
• Long gestation (time windows; ~147 d)
• Interventions possible without abortion
  • Fetal intervention studies (catheterisations)
• Off-spring at birth: comparable to the human
  • Last trimester interventions
Fetal programming: The sheep as experimental model

Disadvantage:
• **Ruminants** ie. distinctive digestive function
  • Little glucose absorption (SCFA)
  • Tolerate rather low levels of fat in the diet
• Makes **postnatal dietary interventions** difficult to study
  • But **special tricks can be applied**
  • Suckling
    • Esophageal groove reflex
    • **By-pass rumen (liquid feed)**

NORMAL

LOW

(HIGH)

MALNUTRITION

BIRTH

OBESOGENIC DIET

PUBERTY

DIET CORRECTION

ADULTHOOD

HEALTHY

Metabolism
Endocrinology
Slaughter

HIGH FAT (HCHF)

HEALTHY (CONV)
Metabolic, endocrine and fasting tolerance tests – 6 mo + 2 years

1. Intravenous bolus injections of:
   1. glucose, insulin (nutrient surplus)
   2. propionate (hepatic gluconeogenesis; fed+fasted)
   3. fasting (nutrient deficiency)
   4. thyroxine (thyroid hormone axis)

2. Blood sampling at specific time points after injections OR onset of fasting
6 months old lambs

• By the end of the period of differential postnatal feeding
Growing lambs (6 months):

HCHF

Fat% in soft tissue in HCHF: ~ 30 (obese)

CONV
Visceral:subcutaneous fat ratio (6 mo) (CT scanning)

Norm | LOW

Prenatal LOW + Postnatal HCHF:
- Worst case scenario: ↑ Visceral adiposity
- ↓ Subcutaneous expandability?

Humans:
- Insulin insensitivity
- Metabolic syndrome

Glucose tolerance test - 6 mo:
Worst case = glucose intolerant

Low:
• Insulin insensitive
• Pancreatic stress↑?

HCHF:
• Insulin secretion ↓
• Insulin sensitivity↑

Low/HCHF:
• Glucose intolerant
• Adaptation conflict!

Fat distribution patterns

Prenatal overnutrition and undernutrition:
- lower deposition of subcutaneous adipose tissue
- associated with visceral adiposity

Khanal et al. (2014) Acta Physiologica 210, 110-126
Gene expression (subcutaneous fat)

Prenatal overnutrition and undernutrition:
- ↓ Fatty acid transport (Fatty acid binding protein 4)
- ↓ Vasculogenesis/angiogenesis (Vascular endothelial growth factor A)
- ↓ Fatty acid release (Hormone sensitive lipase)

Khanal et al. (In preparation)
Subcutaneous adipose tissue - 6 mo. (H&E staining)

Prenatal Norm

Postnatal CONV

Postnatal HCHF

Low/CONV:
- More premature adipocytes?
- Predisposing for visceral adiposity?
- Hyperplasia?
- Hypertrophy?
Cell no. index: Non-obese state

**HIGH** and **LOW**

**NORM**

Prenatal **overnutrition** and **undernutrition**:

- Reduce **non-obese cellularity** in subcutaneous and mesenteric fat

Khanal et al. (In preparation)
Prenatal overnutrition and undernutrition:

- ↓ Obesity-induced hyperplasia in subcutaneous, mesenteric and particularly perirenal fat
- ↑↑ Obesity-induced hypertrophy in perirenal fat
- In LOW also in mesenteric fat
2-2½ years adult sheep

• After 1½ - 2 years on a moderate diet
• HCHF: body fat correction
Insulin tolerance test - adults: Insulin response

**Prenatal:** Low

- **Insulin insensitive**!
- Amplified in HCHF (tendency)
  - Higher AUC insulin
- Glucose tolerance unaffected

Plasma T3 and T4 (age)

Total T3

Thyroid hormone axis function: Young adult sheep

Thyroid hormone axis function: Young adult sheep

LOW: Hyperthyroid as adults

Thyroid hormone signalling:
- Increased in liver+muscle
- Increased energy expenditure?
- Decreased in adipose

Endocrine adaptive responses to fasting – adult sheep

Endocrine adaptive responses to fasting - adult sheep

- Leptin dysregulation during fasting
- Dysregulation of all endocrine systems under hypothalamic-pituitary control

Hypothalamus:
- Main target organ of leptin
- Regulator of reproductive function

Subcutaneous adipose tissue (H&E staining) – 24 mo. – prenatal LOW

Low-CONV
Low-HCHF
Norm-CONV
Norm-HCHF

Hou et al. In preparation
Fetal programming complex?
What have we learnt from sheep?

1. Malnutrition in late fetal life:
   1. Reduces birth weight ("marker" – but bad one)
   2. Growth stops earlier (smaller adult body size)
   3. Development of important organs is affected
      1. (Subcut.) adipose, liver, thyroid, (adrenals)
      2. Not muscle! (Hou et al. 2014. PLoS ONE 8, 6, e65452)
4. Metabolic and endocrine function changed
   1. Glucose-insulin axis
   2. Hypothalamus-pituitary controlled systems:
      Thyroid hormones, GH-IGF-1, corticosteroids
   3. Adipose-leptin dysregulation ↔ hypothalamus?
   4. Increasingly manifested with age
What have we learnt from sheep?

2. Impacts of an unhealthy diet after birth:
   1. Can to a remarkable extent be corrected by diet and body fat correction later in life

3. Is birth a critical set-point for many permanent programming effects (precocial animals)?
Management strategies

✔ **Prevention**: special attention to peri-conceptional and pre-partum nutrition = periods with greater risk of programming

✔ **Avoid negative production implications**: slaughter animals before adulthood

✔ **Avoid transgenerational transfer**: programmed animals should not be used in reproduction

Reproduction	

• All other hypothalamic-pituitary axes affected
The other contributors:

Faculty of Health and Medical Sciences, University of Copenhagen, DK:
Prabhat Khanal          Bjørn Quistorff
Anna Hauntoft Kongsted  Jens Høiriis-Nielsen
Lei Hou                 Allan Vaag
Anne Marie Dixen Axel   André Chwalibog
Sanne Husted            Haja Kadarmideen
Lærke Johnsen           Semra Gündüz
Vibeke Grøsfjeld Christensen Dennis Schultz Jensen

Technical University of Denmark, DK:
Lars I. Hellgren

NOVO Nordisk A/S, DK
Kirsten Raun            Marina Kjærgaard

Liggins Research Institute, Auckland University, NZ:
Mark Oliver

University of Western Australia, Australia:
Dominique Blache

University of Nottingham, United Kingdom:
Michael Symonds Mark Birtwistle
Questions ?