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Impacts of early life nutrition on fat tissue morphology and gene expression in adult sheep

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Introduction

- It is quite well-established that adult obesity and a wide range of metabolic-endocrine disorders can have a fetal origin and can be predisposed by both undernutrition and overnutrition in late fetal life.
- The underlying mechanisms are, however, far from understood.

Hypotheses:

- Adipose tissues are differentially programmed by over- compared to undernutrition in late fetal life.
- The phenotypic manifestation of this programming in adipose tissue of adults is tissue specific.
- Ability of adipose tissues to recover from development of obesity in early postnatal life relies on the prenatal nutritional history.

Objectives

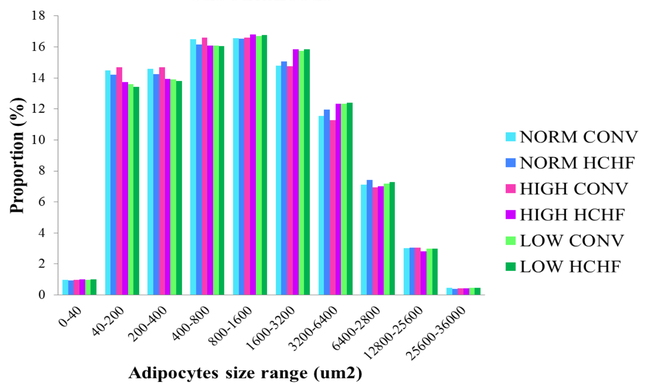
- To assess the long term implications of late gestational under- and overnutrition as well as exposure to an early postnatal obesogenic diet on morphological changes and gene expression patterns in subcutaneous, perirenal and epicardial adipose tissue in adult sheep.
- To investigate whether these impacts of late gestation malnutrition and early postnatal adipocity can be reversed by dietary correction later in life.

Results (long-lasting impacts of early life malnutrition)

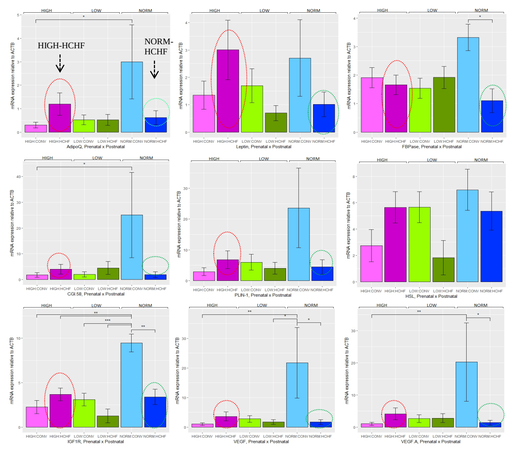
Subcutaneous adipose tissue:* *Fetal malnutrition changed male phenotype in female direction

- ***Long-lasting prenatal malnutrition impacts :***
  - Lasting changes in expression of adipogenic genes were more pronounced in males than females, and changed males in a female phenotype direction (not shown).
  - No long-term impacts were observed on adipose morphology including size distribution (A).
- ***Long-lasting impacts of early postnatal obesity and pre- postnatal nutrition interactions:***
  - No long-term impacts on adipose morphology were detected.
  - HIGH sheep exposed to overnutrition in late fetal life appeared to attain tolerance towards adverse effects of an early postnatal obesogenic diet (HCHF) on gene expression patterns (B).

(A)



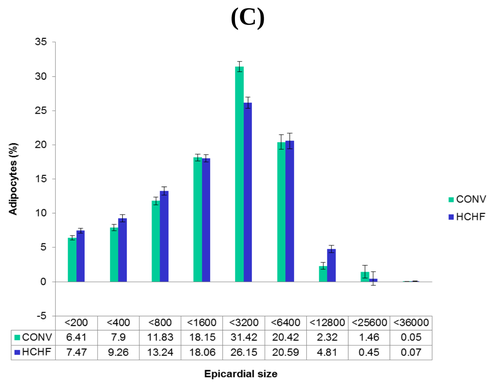
(B)



Epicardial adipose tissue:* *Only affected by postnatal nutrition

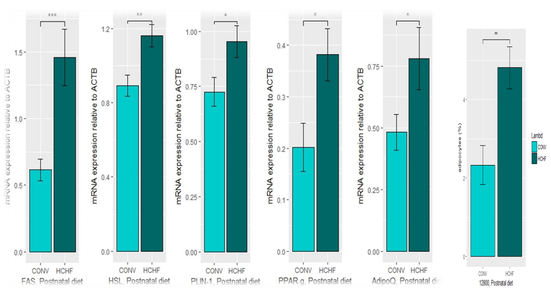
- ***Long-lasting prenatal malnutrition impacts:***
  - Not detected for any of the studied parameters.
- ***Long-lasting impacts of early postnatal obesity (after 2 years feeding of a non-obesogenic diet):***
  - Cell distribution patterns were shifted towards larger cells (C).
  - This was associated with up-regulation of adipogenic and lipid metabolism genes (D).

(C)



	<200	<400	<800	<1600	<3200	<6400	<12800	<25600	<36000
CONV	6.41	7.9	11.83	18.15	31.42	20.42	2.32	1.46	0.05
HCHF	7.47	9.26	13.24	18.06	26.15	20.59	4.81	0.45	0.07

(D)



Conclusion

- Long-lasting impacts of late fetal undernutrition and early postnatal overnutrition on adipose tissue traits were tissue and sex specific.
- Epicardial adipose tissue was exclusively affected by the postnatal diet, probably due to the mismatch in timing of development in this tissue (early gestation) compared to the prenatal nutritional insult.
- Long-lasting impacts of early life nutrition were much more abundant in males compared to females, and appeared to change the male adipose phenotype in a more female direction.
- Surprisingly, exposure to prenatal overnutrition appeared to be associated with increased tolerance towards long-term effects of an obesogenic diet in early post-natal life in subcutaneous but not perirenal adipose tissue.
- Changes in adipose tissue morphology were not closely associated with changes in gene expression and other factors must be involved in changes in adipose cell size distribution.

Experimental design

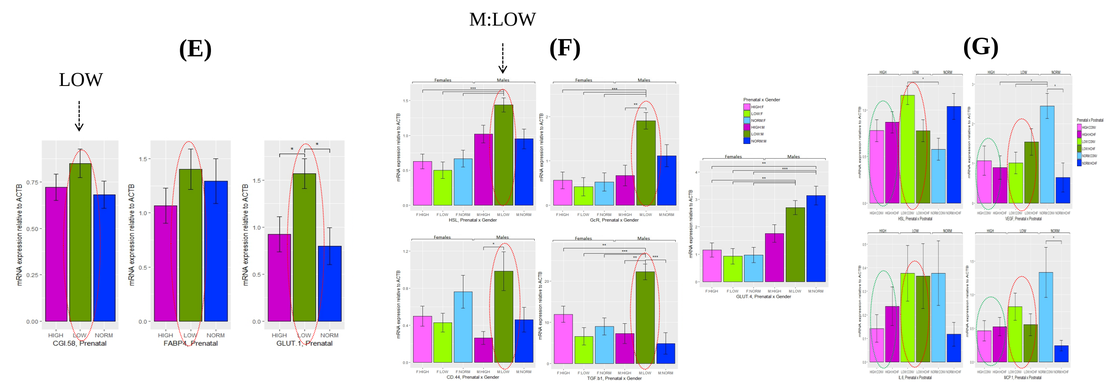
The flow chart of experimental feeding trial

*Prenatal nutrition: Daily provisions in diet for twin-pregnant ewes are indicated as % of NRC recommendations for energy and crude protein (CP).
**Postnatal nutrition:
- CONV: Conventional, moderate diet; :milk replacer and hay (until 8 weeks) thereafter, only hay. Feeding was adjusted weekly to achieve moderate constant growth rates of approximately 225 g/day until 6 months of age.
- HCHF: High-starch-high-fat diet; dairy cream-milk replacer mix (1:1 ratio) and rolled maize.
***All sheep were fed a conventional hay-based diet from 6 months to 2½ years of age.
At 2½ years of age, adipose tissue samples were collected at autopsy to characterize morphology including cell size distribution patterns (Visiopharm®) and mRNA gene expression patterns (qPCR).

Perirenal adipose tissue:* *Most sensitive to early life malnutrition

- ***Long-lasting prenatal malnutrition impacts:***
  - Fetal undernutrition upregulated expression of adipogenic and lipogenic genes (E), but for some genes it was only the case in males (F).
  - Prenatal overnutrition changed adipose cell size distribution in males towards larger cells, ie. a more female-like phenotype (not shown).
- ***Long-lasting impacts of early postnatal obesity:***
  - Gene expression for a range of adipogenic and lipogenic genes were reduced in males exposed to the obesogenic HCHF diet in early postnatal life, ie in a more female direction (not shown).
  - In females, only few long-lasting effects of the early postnatal nutrition on gene expression were observed.
- ***Long-lasting pre-and postnatal nutrition interactions:***
  - Expression patterns for a number of genes changes in opposite direction in fetally undernourished (LOW) as compared to overnourished (HIGH) sheep in response to early postnatal exposure to the obesogenic HCHF diet (G).

(E) **(F)** **(G)**



Acknowledgements

UNIVERSITY OF COPENHAGEN
Centre for Fetal Programming
MINISTRY OF HIGHER EDUCATION
UPM UNIVERSITI PUTRA MALAYSIA BERILMU BERBAKTI
EAAP 2018 69th Annual Meeting of the European Federation of Animal Science Dubrovnik, Croatia, 27th to 31st August 2018

Poster presented by: Sharmila Binti Ahmad at 69th EAAP (2018), Dubrovnik Croatia