Effects of conceptus sex and genetics on circulating TH and IGF in heifers at mid gestation depend on maternal genetic background

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Maternal physiology in pregnancy

- Substantial changes in endocrine milieu and adjustments in carbohydrate, lipid and protein metabolism
- Metabolic adaptations occur in response to hormonal changes associated with fetal nutrient demand and maternal supply essential for fetal growth
- Interindividual variation in metabolic responses to pregnancy has long been recognised
- Environmental or genetic factors ?

Evolution, fitness and ideas

- Maternal genome and conceptus genome have shared interests but are also in conflict
  (Haig 1993, Q Rev Biol 68:495-532)

- Fetal-maternal communication is via the placenta
  (Haig 1996, J Evol Biol 9:357-380)

- Reprod Dom Anim **38**, 276–289 (2003)

  ISSN 0936-6768

  Embryo-Maternal Communication in Bovine – Strategies for Deciphering a Complex Cross-Talk

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Animal resources and previous work

Embryo-fetal and maternal resource

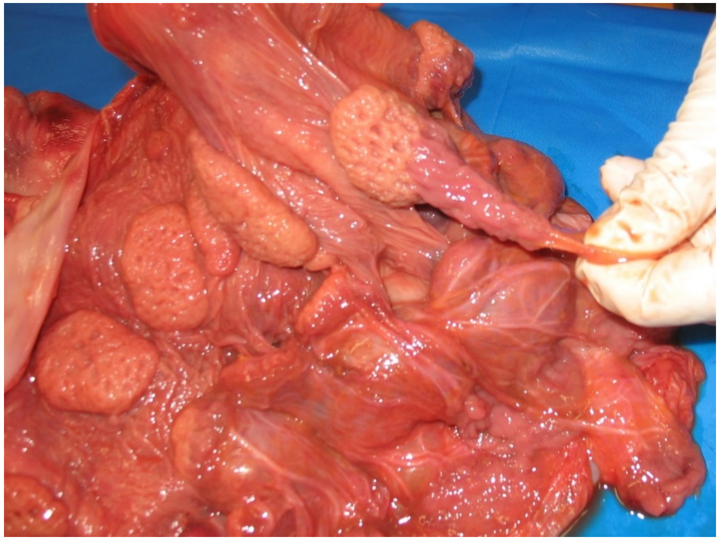
Bos taurus taurus (**Bt**)

Bos taurus indicus (**Bi**)

- 16-20 month old heifers, managed as one herd
- **Purebred and reciprocal cross concepti (n = 60, 100)**
- **Concepti, maternal blood at Day 48 and 153 of gestation**
- Phenotype including hormone profiles, clinico-chemical screen
- Embryo-fetal growth driven by the conceptus

Role of the placenta

- Direct interaction of maternal and conceptus genomes, nutrient provision - extraction



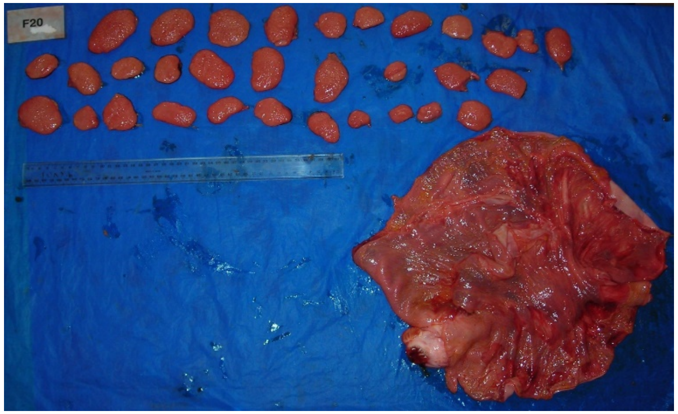
Placenta materna and *fetalis* in bovine Day 153 pregnancy

- Significant source of hormones such as placental lactogen and prolactin-related proteins, with growth hormone and prolactin like activity (Gootwine 2004, Anim Reprod Sci 82:551-556)

- The placenta drives fetal growth and development, and is a major factor in modifying maternal environment

Significant variation in placental phenotype

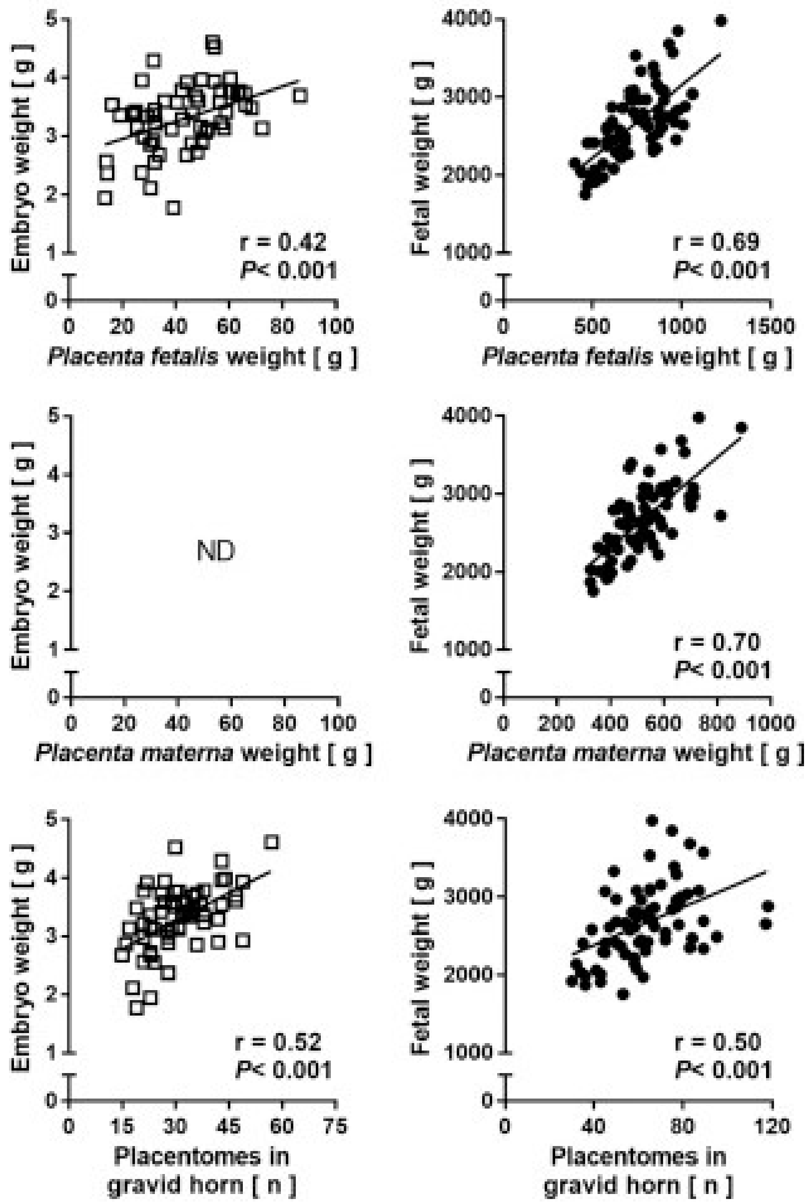
Day 153 resource collection



Placenta and embryo-fetal growth

Day 48

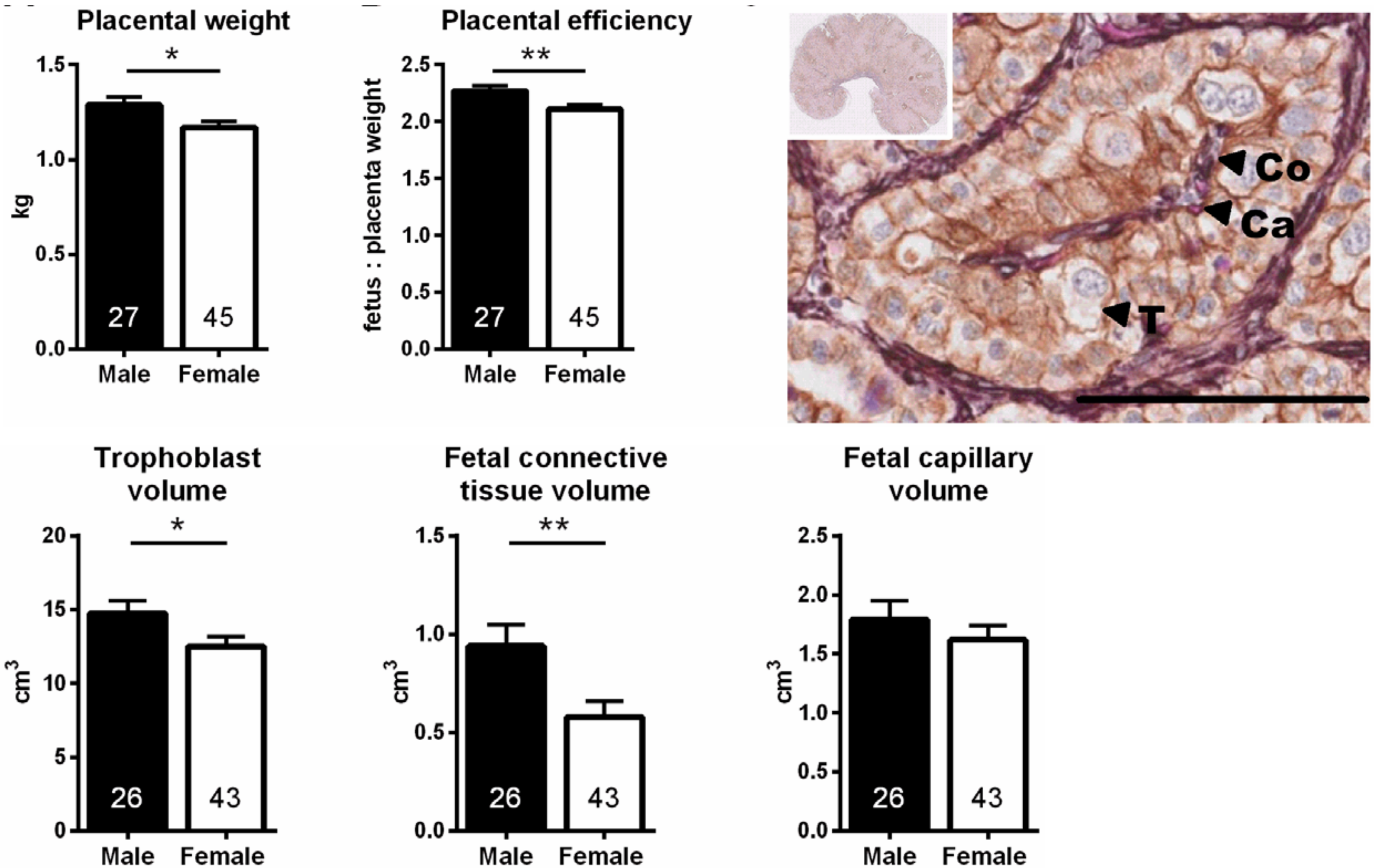
Day 153



Estrella et al. 2017, Placenta 55:37-46

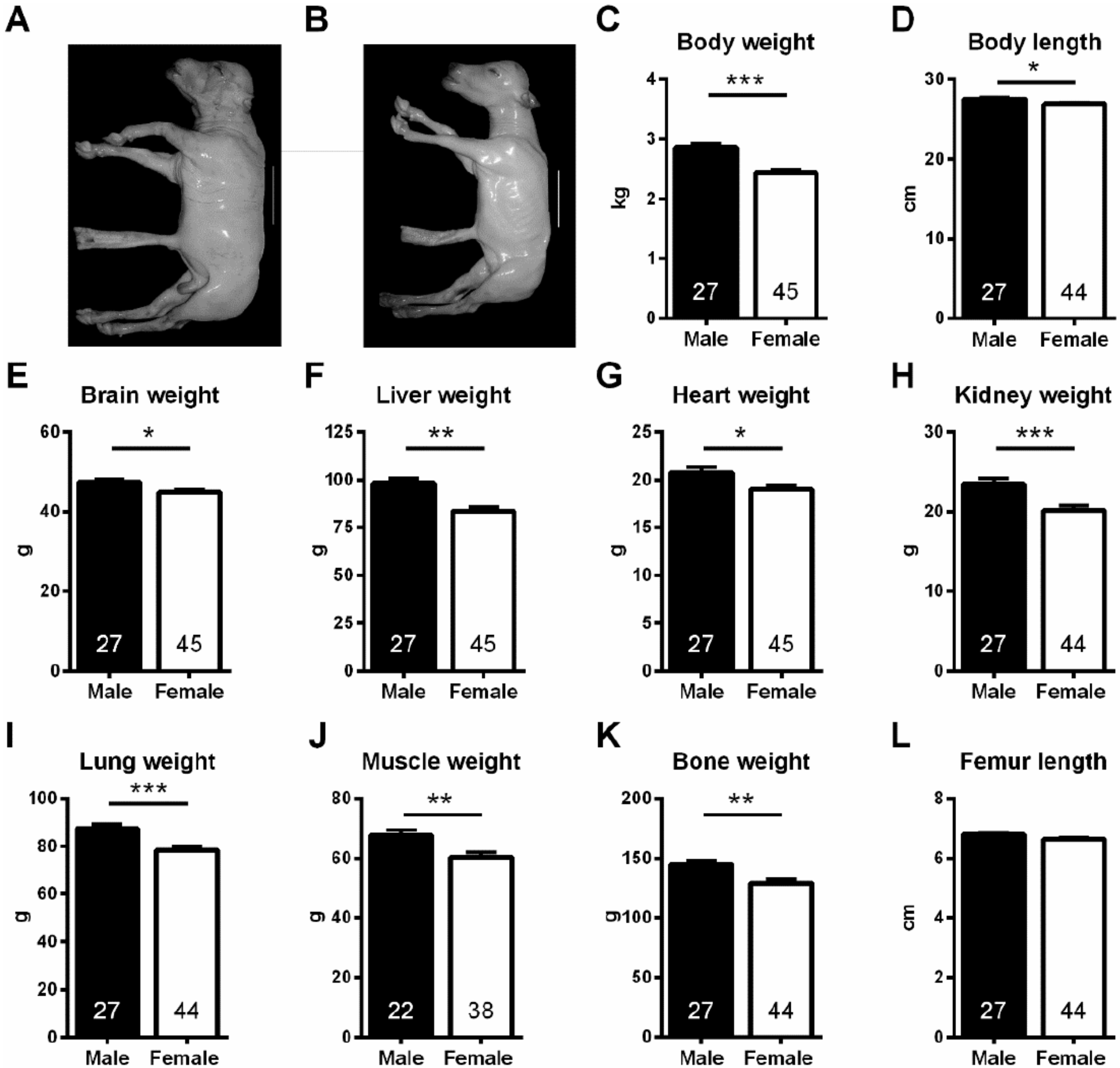
The placenta is sexually dimorphic

Day 153 of gestation



Estrella et al. 2017, submitted

… as is the fetus



Day 153 of gestation

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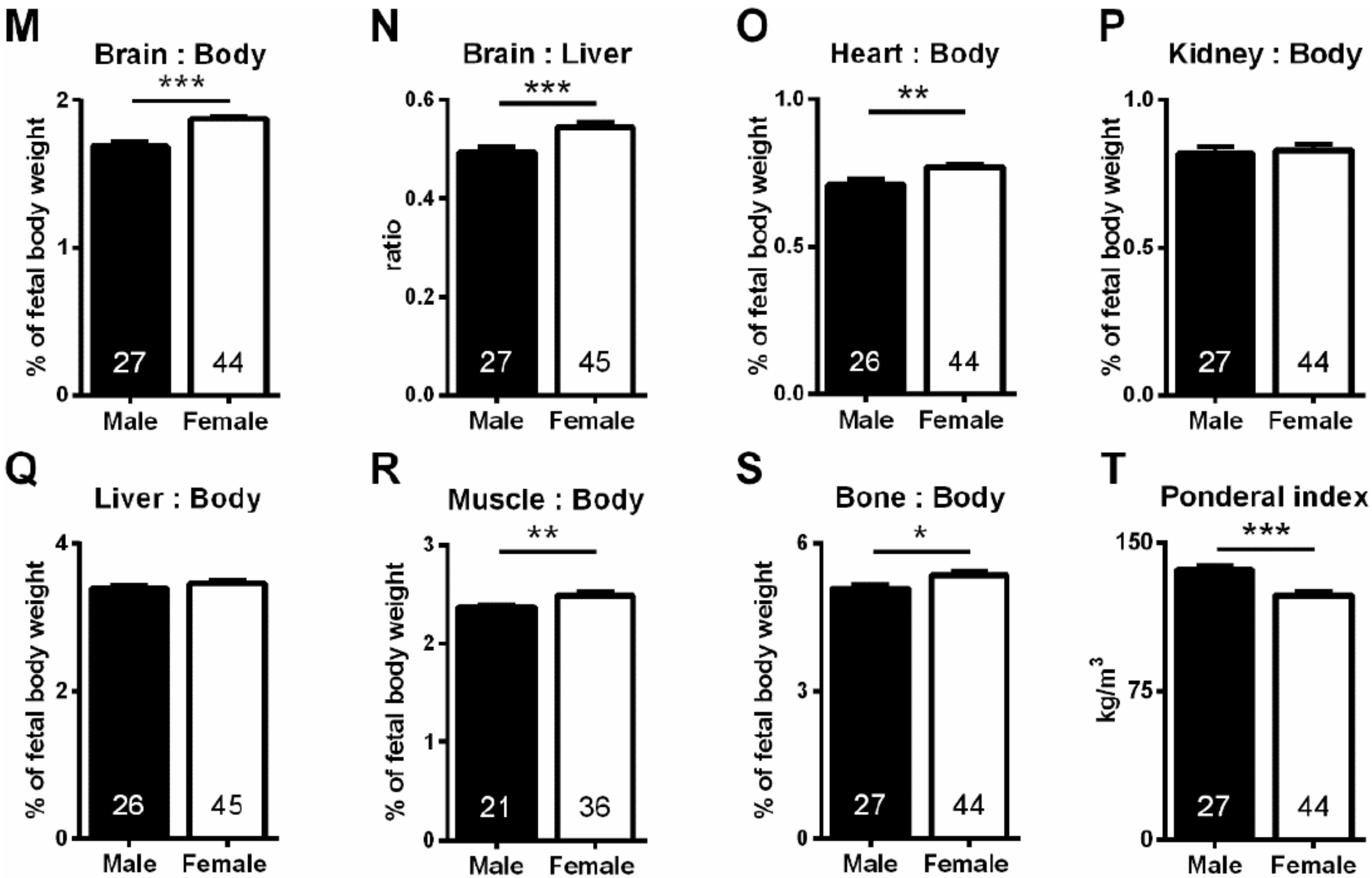
Sex-specific fetal growth strategies

Day 153 of gestation



Estrella et al. 2017, submitted

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PLoS one

INSL3 in the Ruminant: A Powerful Indicator of Gender- and Genetic-Specific Feto-Maternal Dialogue

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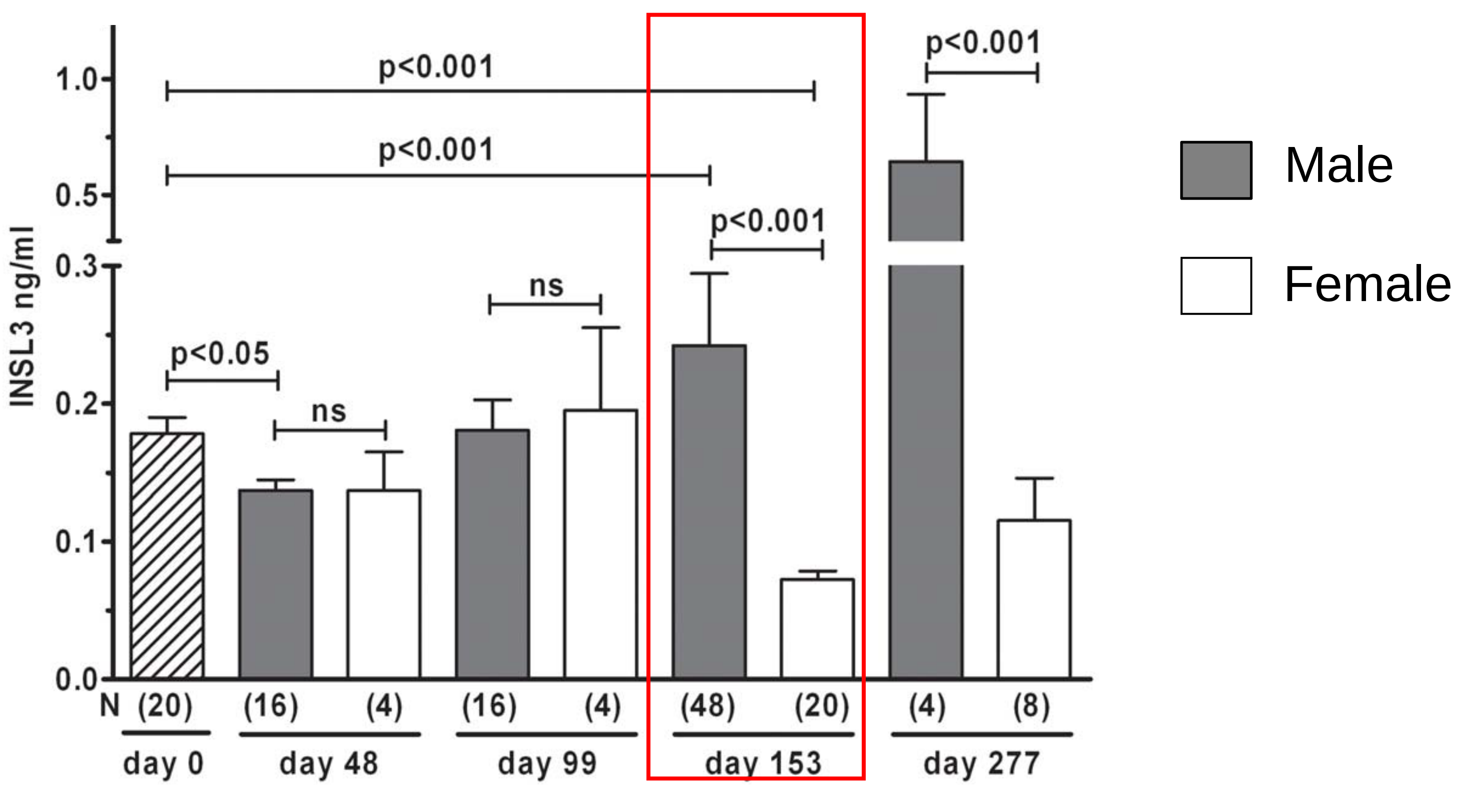
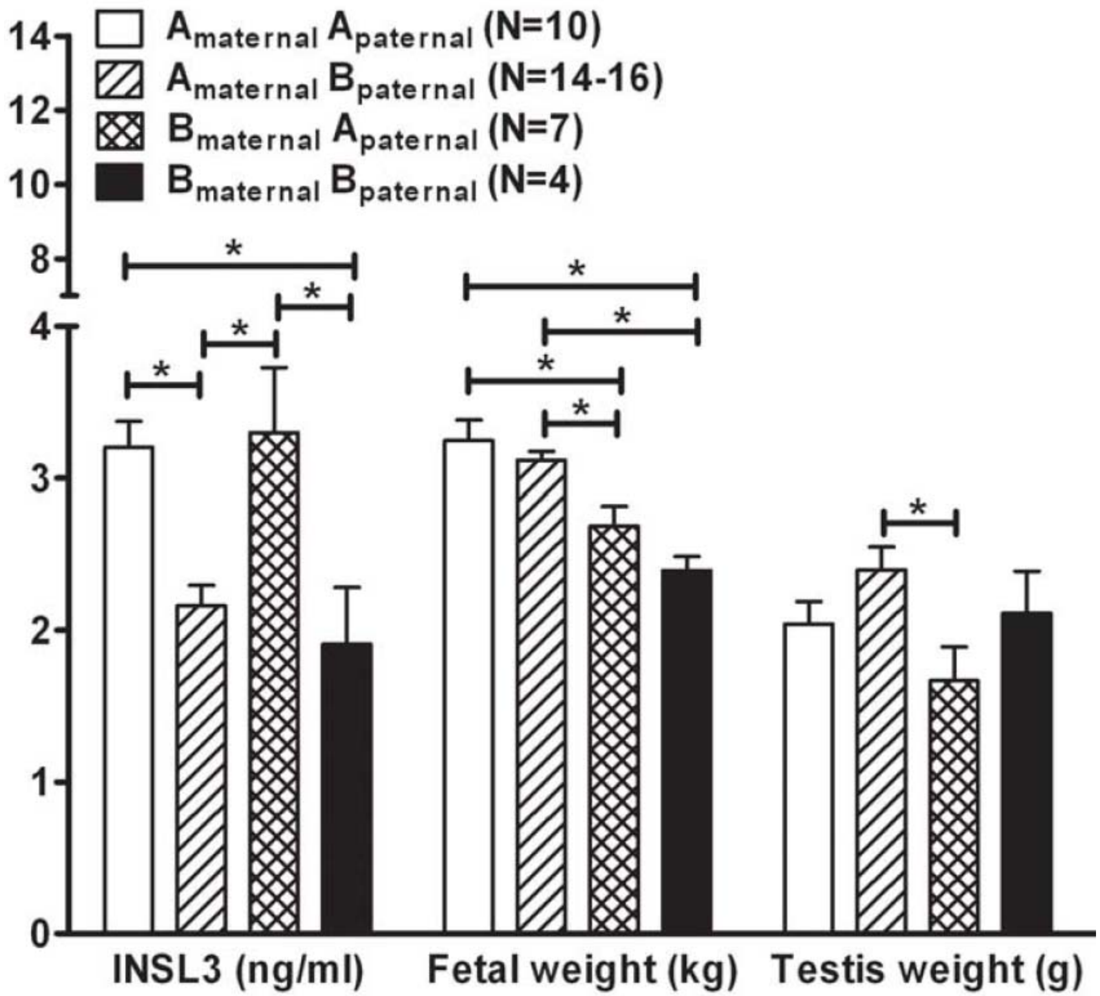
Insulin-like peptide 3 in maternal serum



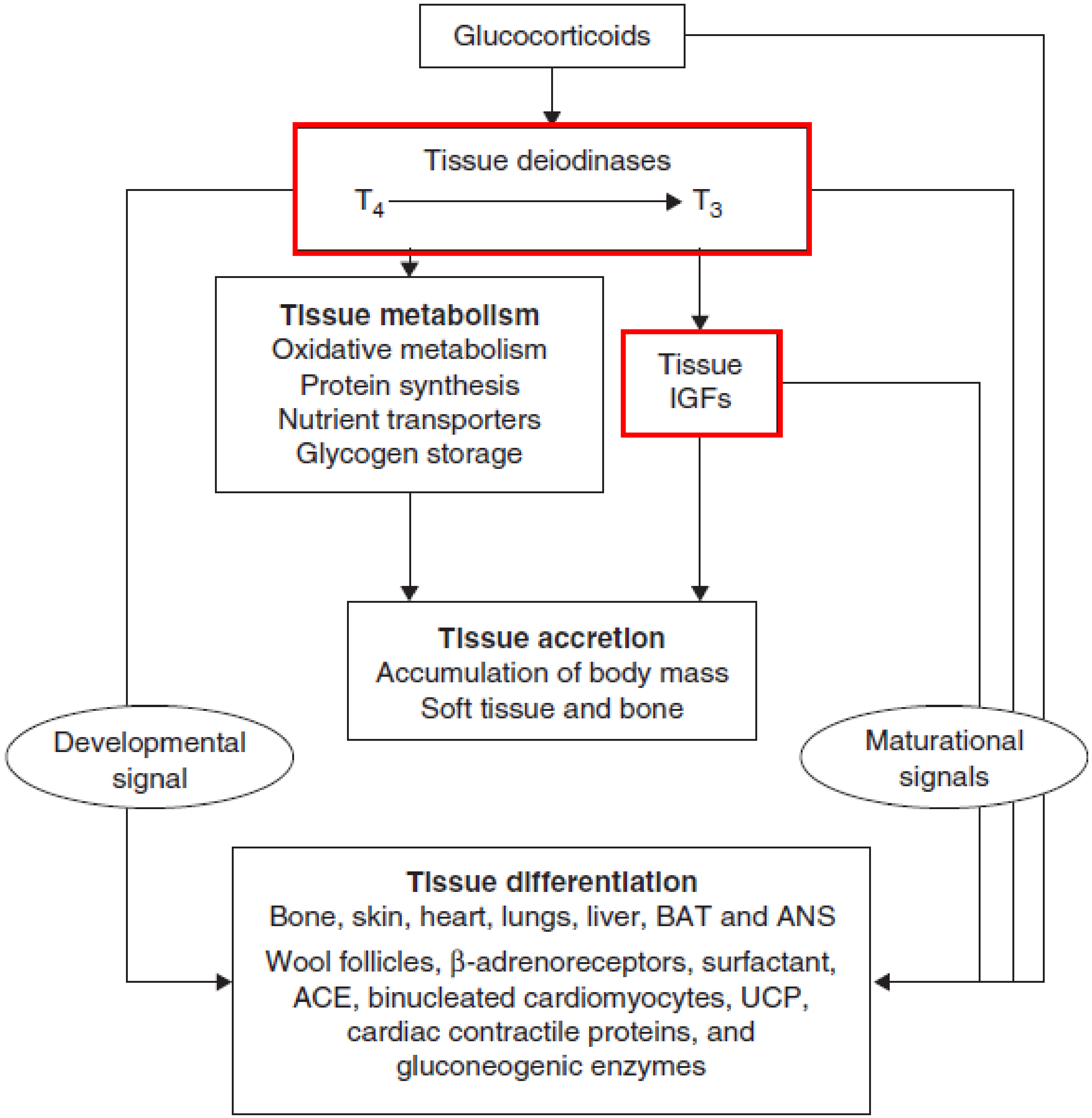
Genetic differences in fetal INSL3



Anand-Ivell and Hiendleder et al. 2011, PLoS ONE 6(5) e:19821

Thyroid hormones and insulin-like growth factors

THs and IGFs in growth and development



Forhead and Fowden 2014, J Endocrinol 221:R87

TH and IGF assays

- Total thyroxine (T4), free thyroxine (fT4), total triiodothyronine (T3) and free triiodothyronine (fT3) assayed using coated tube radioimmunoassay IM 1447, IM 1363, IM 1699 and IM 1579 (Immunotech/Beckman Coulter, Prague, Czech Republic). Reverse triiodothyronine (rT3) assayed using reagents from double antibody radioimmunoassay kit BC 1115 (Biocode-Hycel, Liege, Belgium).

- Insulin-like growth factor 1 and 2 (IGF1, IGF2) and total IGF binding proteins (tIGFBPs) were measured by RIA following separation of IGFs and IGFBPs by size-exclusion HPLC under acidic conditions as described previously. Total IGFBPs obtained here is reflecting the total amount and binding affinity of IGFBPs present in plasma.

  (Sullivan et al. 2009, J Anim Sci 87: 3304-3316)

Statistical analyses

- Angus and Brahman dam parameters analysed separately with GLM procedures in SPSS using the model:

$$y_{ij} = Intercept + S_i + C_j + S_i \times C_j + MW + MaxT + MinT + e_{ij}$$

y_{ij} : Maternal parameter

S_i : Conceptus sex (i = male, female)

F_j : Conceptus genetic effect, for Bt dams (j = BtxBt, BixBt)
for Bi dams (j = BixBi, BtxBi)

$S_i \times F_j$: Interaction between conceptus sex and genetics

MW : Maternal weight at slaughter
MaxT : Maximum temperature at day of slaughter
MinT : Minimum temperature at day of slaughter

Effects of conceptus sex and genetics on maternal hormones - Angus

Table 1. ***R*-squared values and significance of linear models, factors and covariates for *Bos t. taurus* (Angus) maternal circulating hormones at Day 153 of gestation.**

	Model		Factors			Covariates		
			Fetal genetics	Fetal sex	Genetics × Sex	Maternal weight	Temp. Max.	Temp. Min.
Parameters	R^2	*P*-value	*P*-value[a]					
Hormones								
Insulin-like growth factor 1 (ng/ml)	0.007	0.878	0.795	0.734	-	-	-	-
Insulin-like growth factor 2 (ng/ml)[b]	0.028	0.553	0.648	0.405	-	-	-	-
Insulin-like growth factor binding protein (%)	**0.220**	**0.018**	**0.764**	**0.710**	**-**	**-**	**0.005**	-
Free thyroxine (pmol/L)	0.103	0.114	0.274	**0.046**	-	-	-	-
Free triiodothyronine (pmol/L)	0.045	0.395	0.225	0.340	-	-	-	-
Reverse triiodothyronine (pmol/L)[b]	0.007	0.884	0.702	0.831	-	-	-	-
Total thyroxine (nmol/L)	**0.375**	**<0.001**	**0.975**	**0.049**	**-**	**-**	**<0.001**	**0.011**
Total triiodothyronine (nmol/L)	0.140	0.106	0.568	0.712	-	-	0.049	-

Effects of conceptus sex and genetics on maternal hormones - Brahman

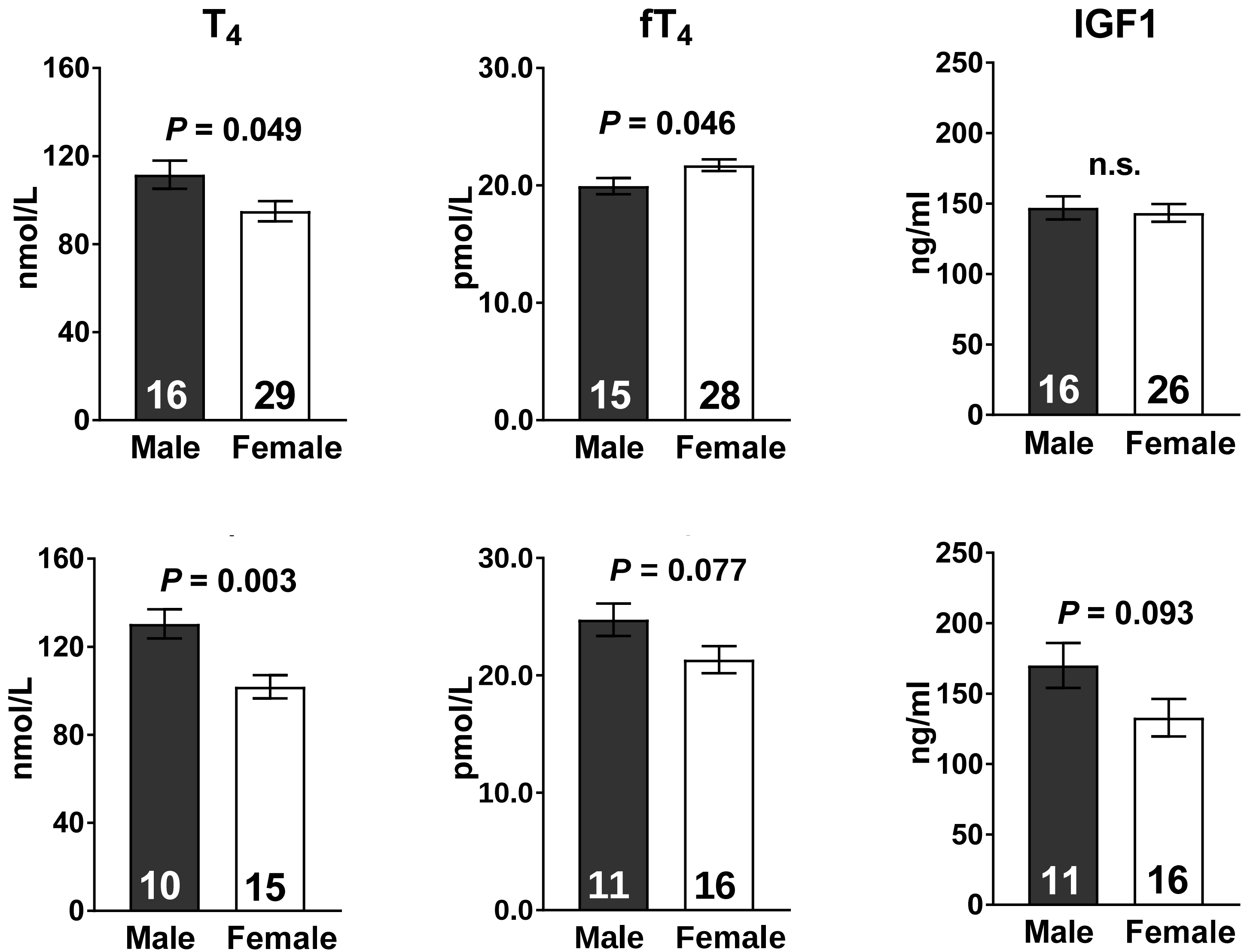
Table 2. ***R*-squared values and significance of linear models, factors and covariates for *Bos t. indicus* (Brahman) maternal circulating hormones at Day 153 of gestation.**

	Model		Factors			Covariates		
			Fetal genetics	Fetal sex	Genetics × Sex	Maternal weight	Temp. Max.	Temp. Min.
Parameters	R^2	*P*-value	*P*-value[a]					
Hormones								
Insulin-like growth factor 1 (ng/ml)	**0.230**	**0.043**	**0.144**	**0.093**	-	-	-	-
Insulin-like growth factor 2 (ng/ml)	0.041	0.607	0.527	0.563	-	-	-	-
Insulin-like growth factor binding protein (%)	0.006	0.930	0.712	0.979	-	-		-
Free thyroxine (pmol/L)	0.132	0.183	0.989	0.077	-	-	-	-
Free triiodothyronine (pmol/L)	0.042	0.608	0.964	0.342	-	-		-
Reverse triiodothyronine (pmol/L)	**0.374**	**0.028**	**0.066**	**0.942**	-	-	-	**0.019**
Total thyroxine (nmol/L)	**0.562**	**<0.001**	**<0.001**	**0.003**	-	**0.027**	-	-
Total triiodothyronine (nmol/L)	**0.552**	**0.001**	**0.527**	**0.387**	-	**0.027**	-	**0.001**

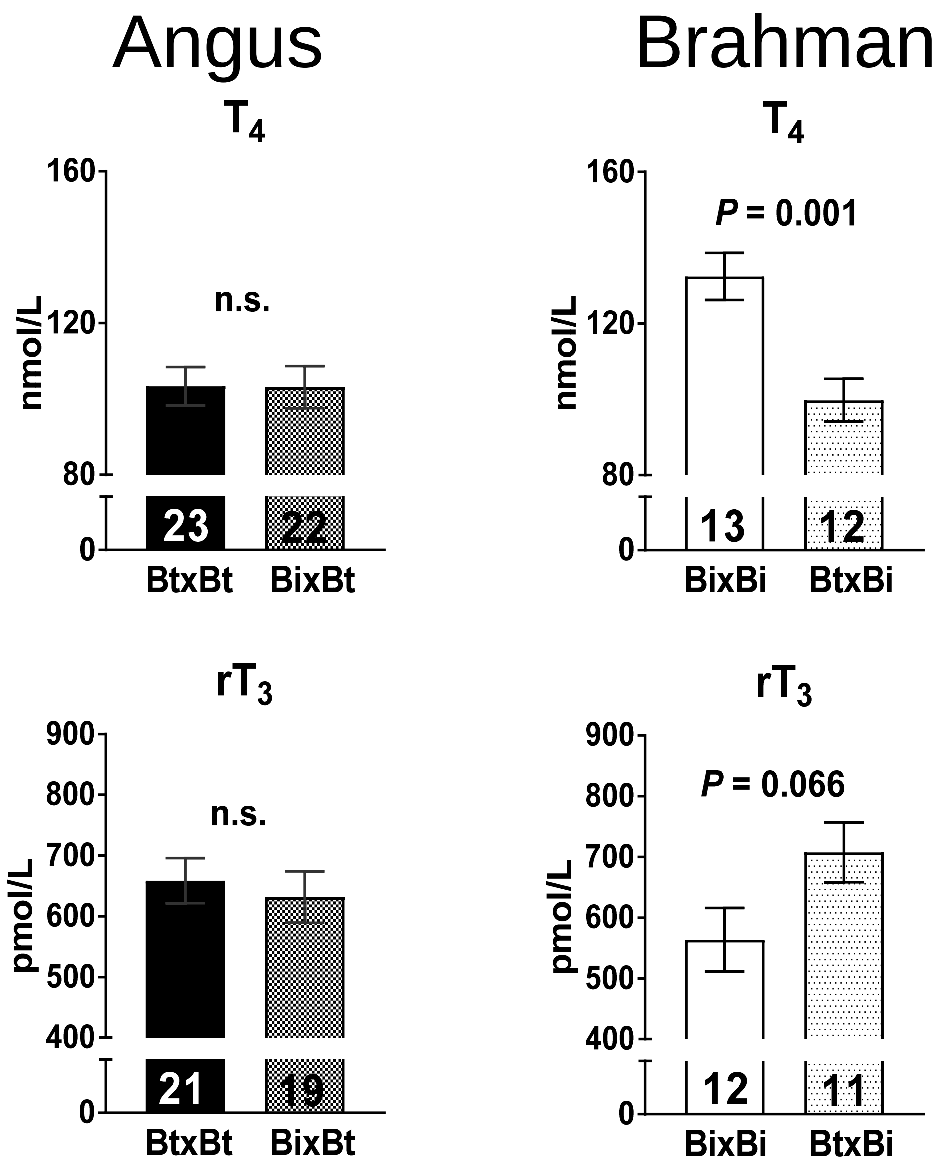
Magnitude of sex effects on maternal hormones

Angus

Brahman

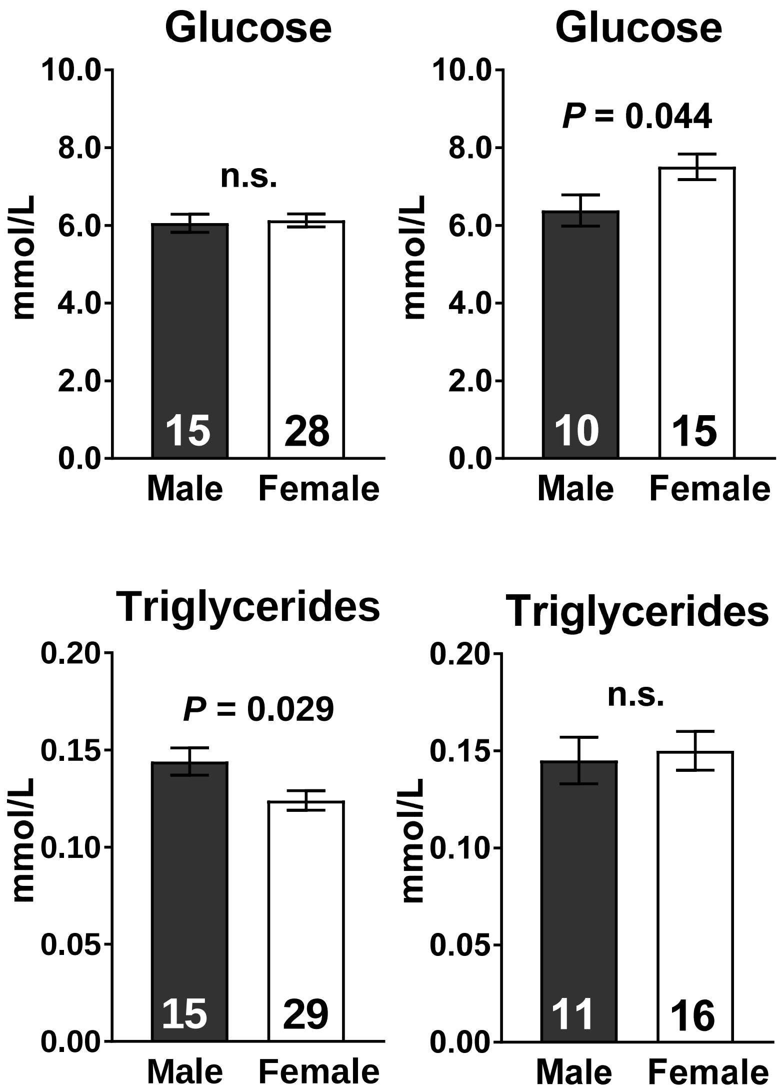


Magnitude of genetic effects on maternal hormones



Sex effects on metabolites

Angus | Brahman



Sex of offspring influences metabolism during early transition period in dairy cows

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Received: 24 October 2014 – Accepted: 23 January 2015 – Published: 4 March 2015

Relevance

Fetal growth, maternal growth, lactation

- Thyroid hormones and insulin-like growth factors affect embryo-fetal growth, postnatal growth and lactation

Regulation of Mammary Gland Sensitivity to Thyroid Hormones During the Transition from Pregnancy to Lactation

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Danish Holsteins Favor Bull Offspring: Biased Milk Production as a Function of Fetal Sex, and Calving Difficulty

Kaare Græsbøll[1]*, Carsten Kirkeby[2], Søren Saxmose Nielsen[3], Lasse Engbo Christiansen[1]

Holsteins Favor Heifers, Not Bulls: Biased Milk Production Programmed during Pregnancy as a Function of Fetal Sex

Katie Hinde[1,4,5]*, Abigail J. Carpenter[2], John S. Clay[3], Barry J. Bradford[2]

Effect of Calf Gender on Milk Yield and Fatty Acid Content in Holstein Dairy Cows

Amy V. Gillespie[1]*, James L. Ehrlich[2], Dai H. Grove-White[1]

The Effect of Calf Gender on Milk Production in Seasonal Calving Cows and Its Impact on Genetic Evaluations

Melanie K. Hess[1,2]*, Andrew S. Hess[1], Dorian J. Garrick[1,3]

Réseau laitier canadien

Canadian Dairy Network

Is Sex-Biased Milk Production a Real Thing?

Conclusions

- The synepitheliochorial bovine placenta enables extensive fetal-maternal communication with significant effects on the maternal endocrine system
- Conceptus sex and genetics impact hormones and clinical-chemical parameters crucial for growth and development, including the mammary gland, but in a dam genetics dependent manner
- Current data may help explain discrepant results for effects of conceptus sex on milk yield

Acknowledgements

- South Australian Research and Development Institute (SARDI)
- Carolyn Fitzsimmons, Zibby Kruk, The University of Adelaide