



**Claire Wathes**

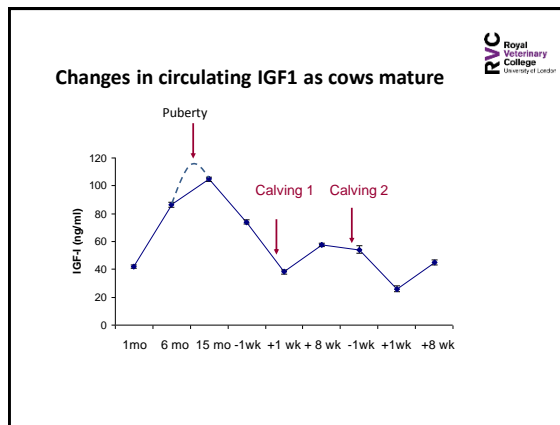
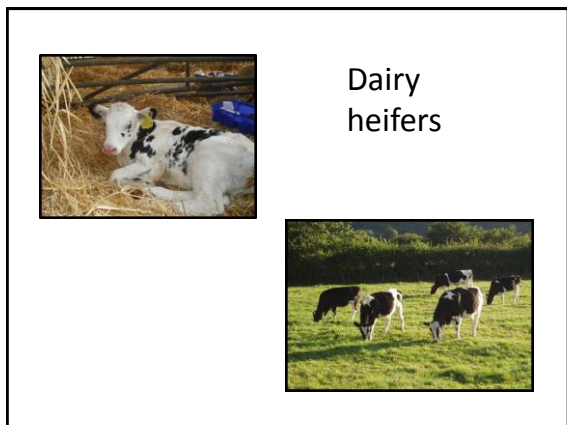
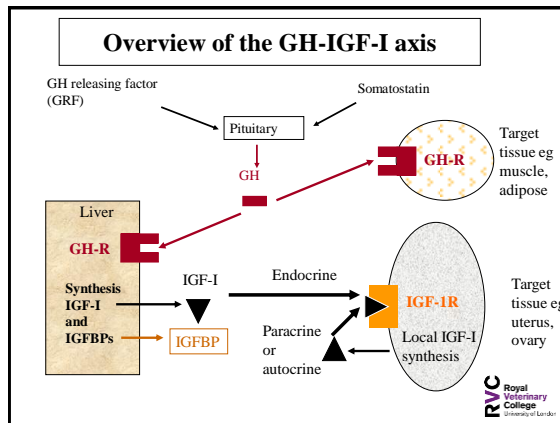
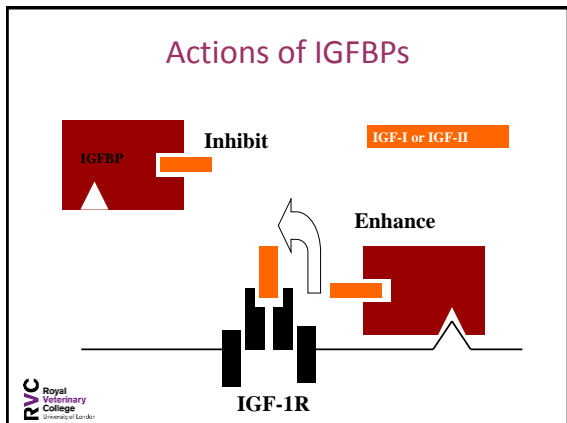
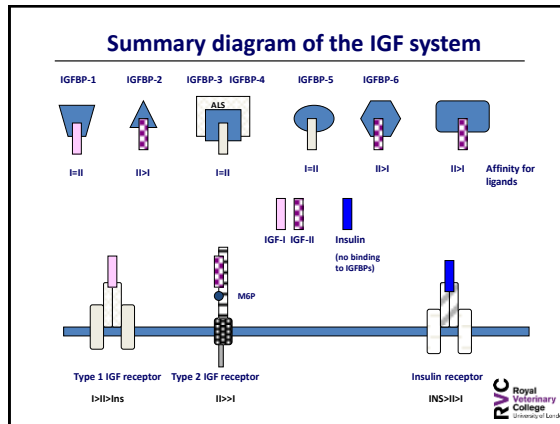
Claire Wathes joined the Royal Veterinary College as Professor of Veterinary Reproduction in 1994, having worked previously at the Babraham Institute, Cambridge and the University of Bristol. Her main research focus is on farm animal reproduction, in particular the causes of infertility in dairy cows: this has led her to study calf growth and development alongside cow nutrition, health and genetics to help understand the contributions these factors all make to successful breeding. She has published over 175 primary research papers and over 50 reviews. She was awarded the Research Medal of the Royal Agricultural Society of England in 2006 and the Marshall Medal of the Society for Reproduction and Fertility in 2015.

A photograph of a green field with several black and white cows grazing. A large tree is on the left, and hills are in the background. The RVC logo is in the top right corner.

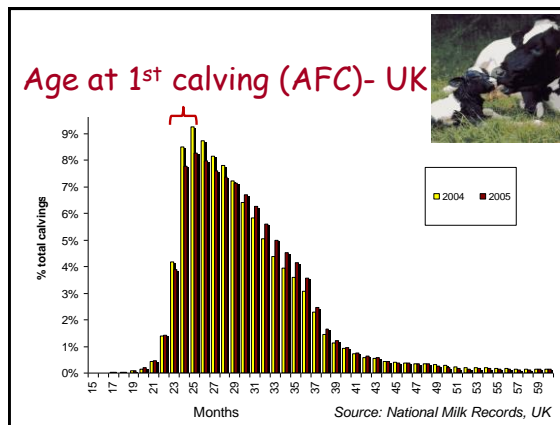
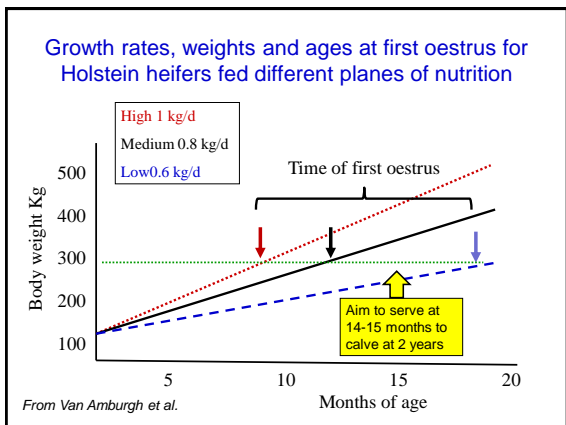
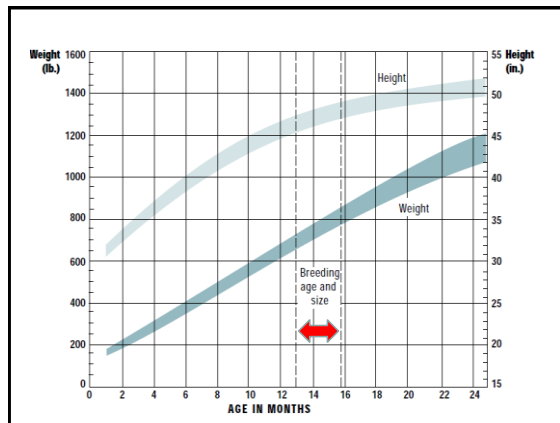
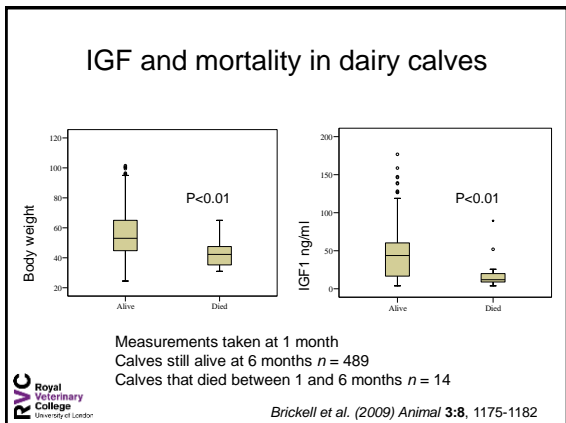
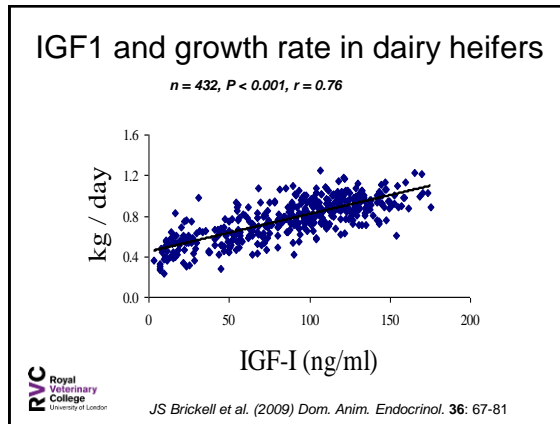
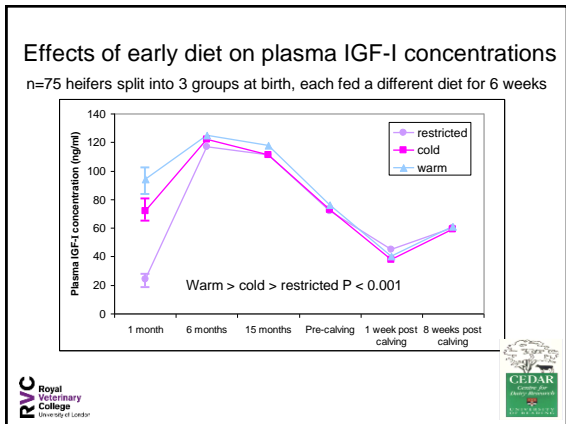
**RVC** Royal  
Veterinary  
College  
University of London

**GH and IGF1 uncoupling-  
consequences and management**  
Professor D Claire Wathes,  
Royal Veterinary College, London, UK

Claire Wathes - GH and IGF1 uncoupling; consequences and management

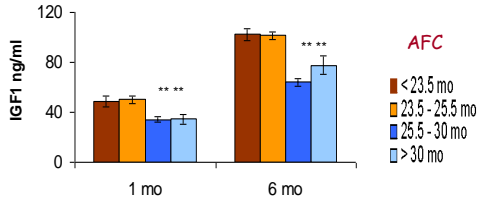


Claire Wathes - GH and IGF1 uncoupling; consequences and management



Claire Wathes - GH and IGF1 uncoupling; consequences and management

Replacement heifers with a delayed AFC are already distinguishable by 1 month of age!



IGF1 is a key growth factor which serves as an indicator of metabolic health.

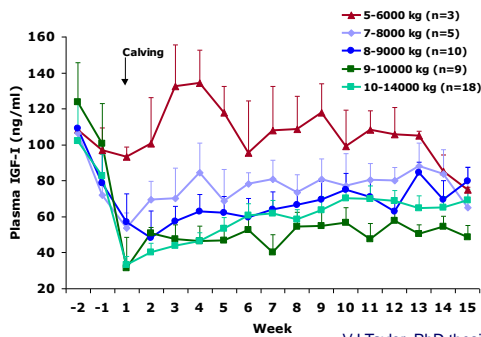
Brickell et al. (2009) Theriogenology 72: 408-416.



Lactating Cows



IGF-I & 305d milk yield



VJ Taylor, PhD thesis



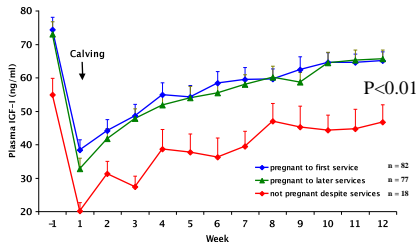
Falkenberg et al. (2008) IGF1 and milk yield

- Studied 417 MP Holstein cows.
- Milked x 3 daily. Herd average 10,300 kg/lactation
- IGF1 measured at 1,4,10,20 & 40 days pp.

Days post partum	Av. 10-d milk	IGF1	r	P
d5-14	31.6 ± 4.8 kg	d1	-0.095	0.46
d5-14		d4	-0.074	0.67
d5-14		d10	-0.106	0.04
d15-24	43.0 ± 5.5 kg	d20	-0.189	<0.01
d25-34	44.0 ± 5.5 kg	d40	-0.165	<0.01

Falkenberg et al. (2008) JDS 91: 3862-3868

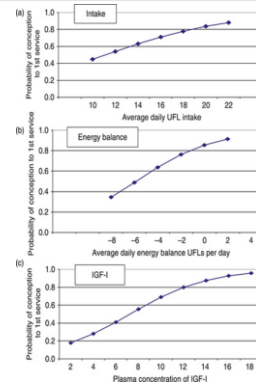
Relationship between IGF-I and conception in multiparous cows



Taylor et al (2004) Vet Rec. 155, 583-588



Metabolic influences on 1<sup>st</sup> service conception rate



J Patton et al. (2006) J Dairy Sci. 89: 1478-1487.

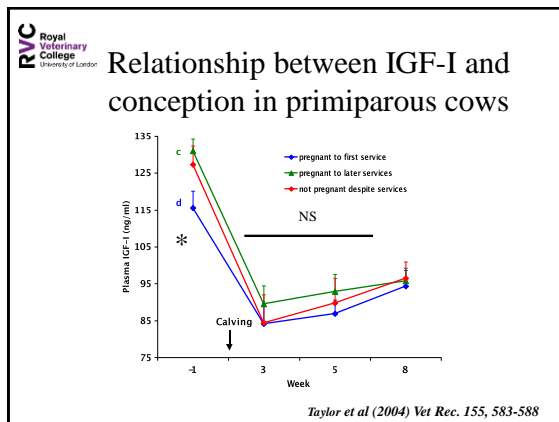
**Claire Wathes - GH and IGF1 uncoupling; consequences and management**

Falkenberg et al. (2008) Relationship between IGF1 and reproductive performance

Trait	1 <sup>st</sup> Q	2 <sup>nd</sup> Q	3 <sup>rd</sup> Q	4 <sup>th</sup> Q
IGF1 AUC ng/ml#	<1975	1985-2395	2396-2840	>2840
n	104	105	104	104
Days to 1 <sup>st</sup> AI	79±21	75±19	77±18	72±19
Days open	117±44 <sup>a</sup>	106±38 <sup>b</sup>	101±37 <sup>b</sup>	98±39 <sup>b</sup>
1 <sup>st</sup> AI	28% <sup>a</sup>	31% <sup>a</sup>	39% <sup>b</sup>	44% <sup>b</sup>
Pregnancy rate	59% <sup>a</sup>	67% <sup>b</sup>	74% <sup>c</sup>	80% <sup>c</sup>

# Composite IGF1 measured at days 1,4,10, 20 and 40 postpartum  
 Animals split into 4 quartiles based on IGF1 AUC  
 a<b<a P<0.05

Falkenberg et al. (2008) JDS 91: 3862-3868



Postpartum IGF1 and culling

Falkenberg et al. (2008) JDS 91: 3862-3868

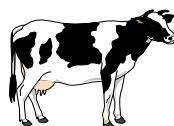
- The proportion of cows culled decreased from the first to the fourth quartile of IGF1 AUC from d1-40 pp: 37%, 27%, 21%, 19%

Lyons et al. (2014) Vet Rec. June 28

- Case control study of cows recruited with LDA. Irrespective of LDA status, the mean IGF1 at recruitment was the only measured parameter associated with subsequent risk of culling: culled 11.7 ng/ml, not culled 23.5 ng/ml P=0.005.



Experimental approach



- Multiparous cows, previous yield 6500 kg

- Pre-calving all fed same diet

Post calving:

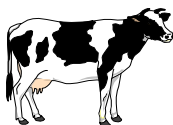
- Mild NEB ad lib grass silage, 8 kg/d dairy concentrate, milked x1 daily, n=6
- Severe NEB 25 kg/d grass silage, 4 kg/d dairy concentrate, milked x 3 daily, n=6

- All animals killed at start of 1<sup>st</sup> follicular wave after calving, approx 14 d postpartum



Tissues used for microarray gene expression studies

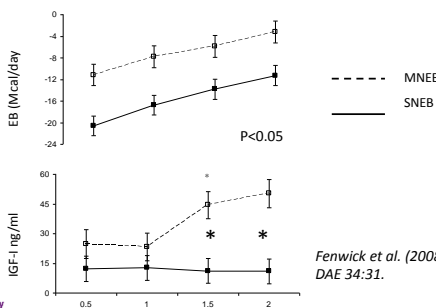
- Liver
- Spleen
- Endometrium
- Oviduct



Blood samples collected for analysis of circulating metabolites, hormones and immune cell populations

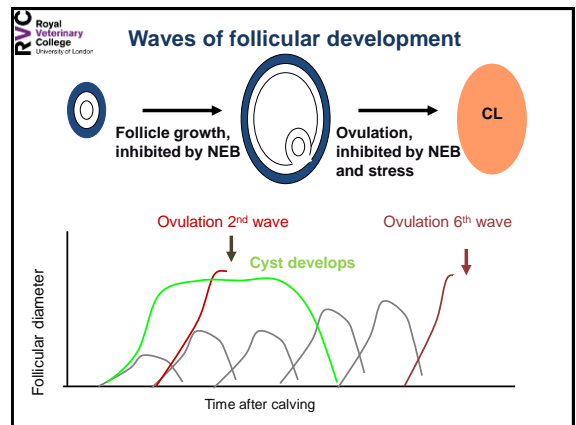
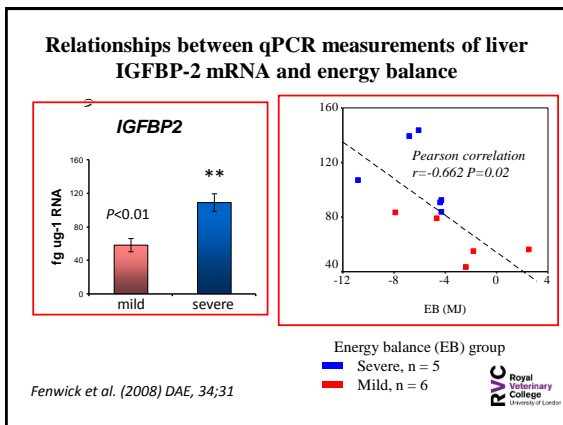
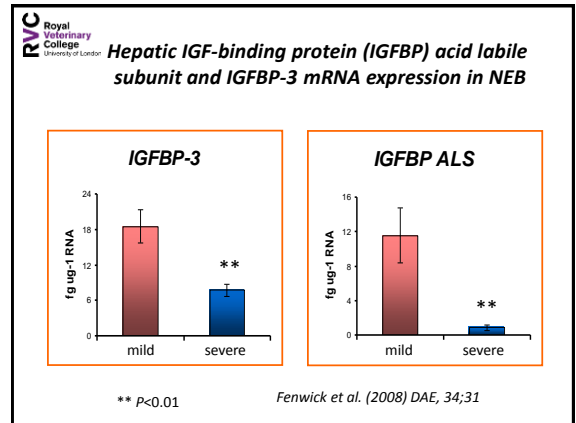
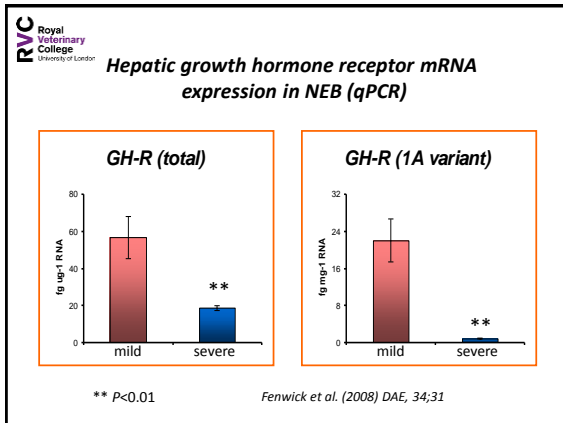
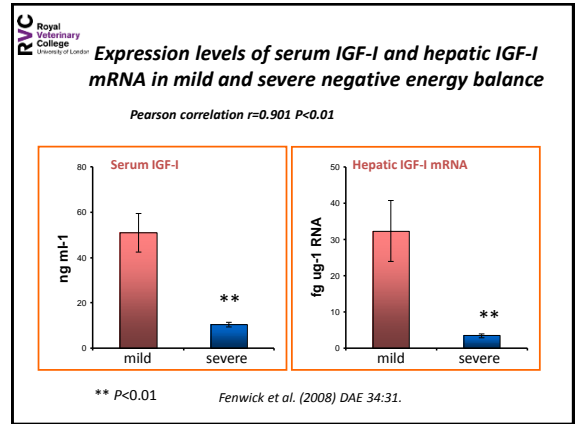
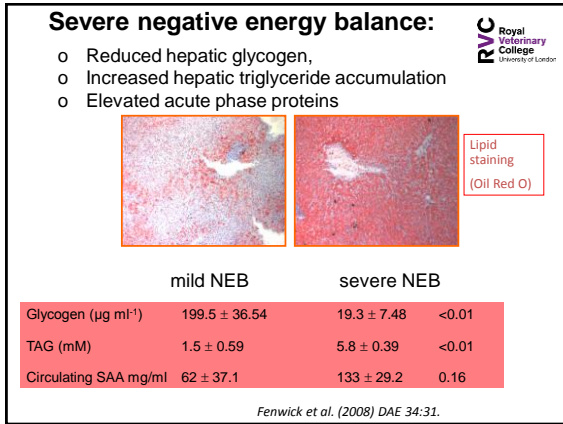


Effect of treatment on EB status and circulating IGF-I in postpartum dairy cows

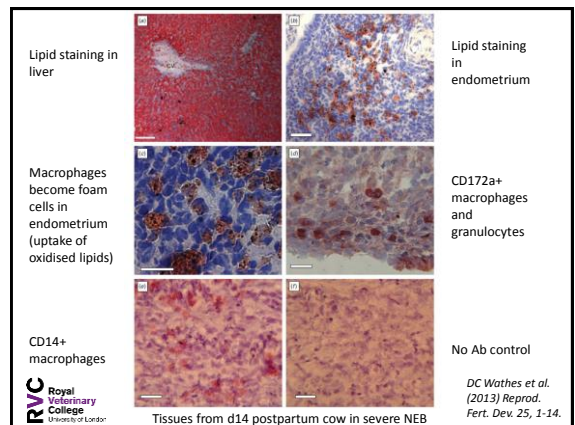
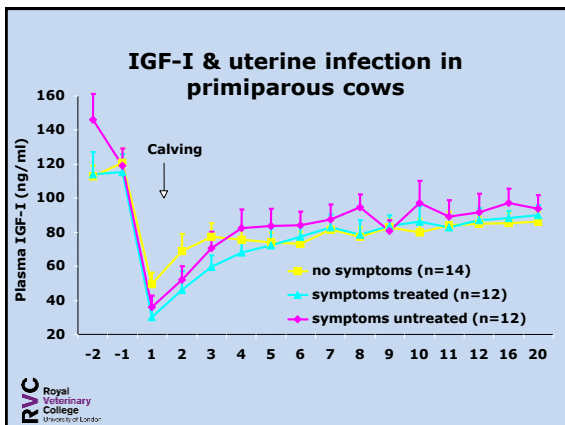
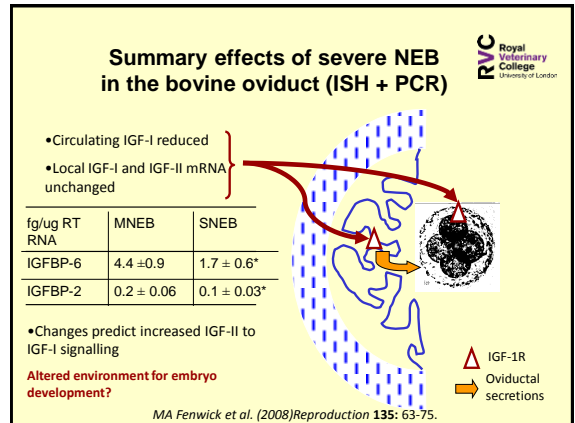
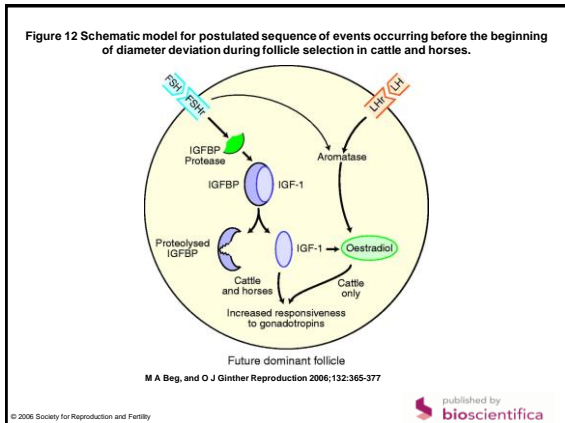
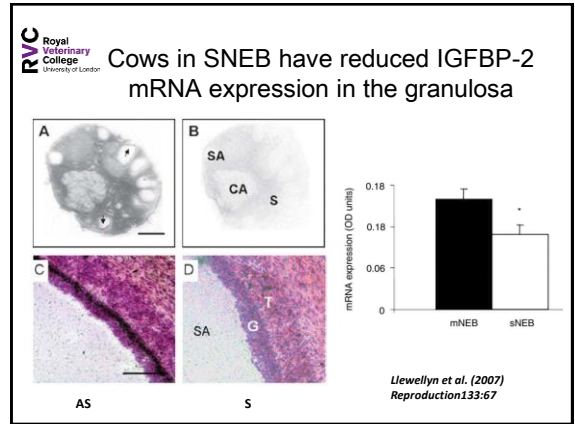
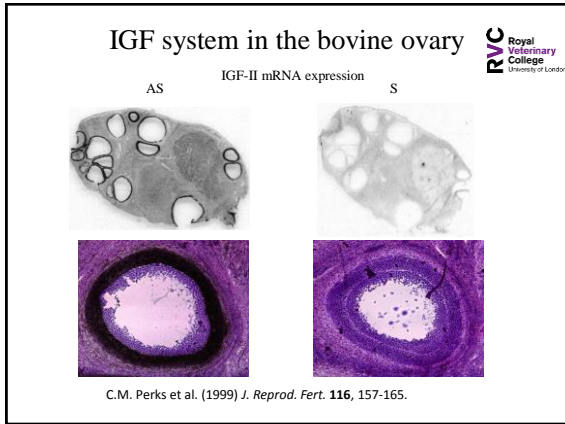




Claire Wathes - GH and IGF1 uncoupling; consequences and management



**Claire Wathes - GH and IGF1 uncoupling; consequences and management**

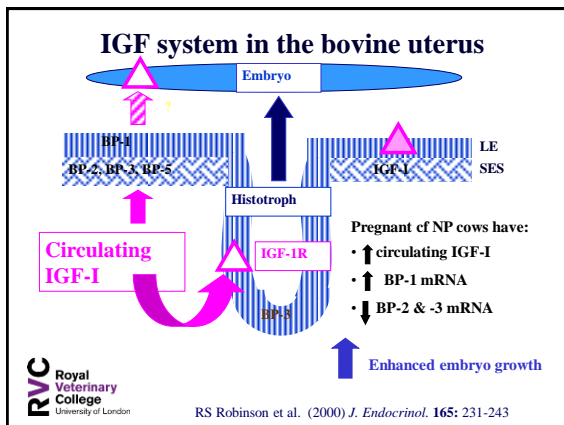
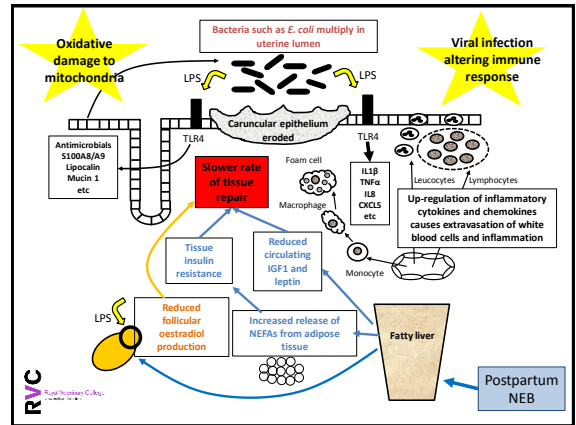
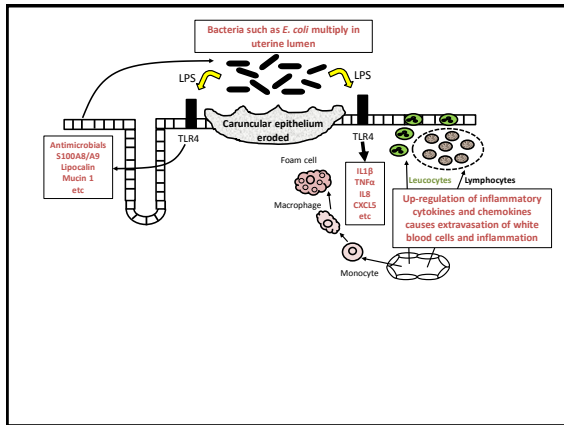
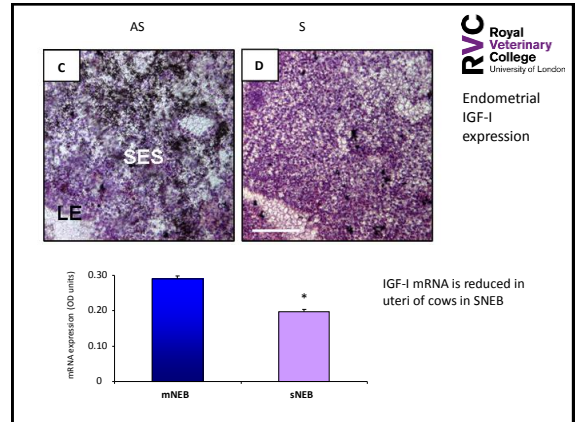


Claire Wathes - GH and IGF1 uncoupling; consequences and management

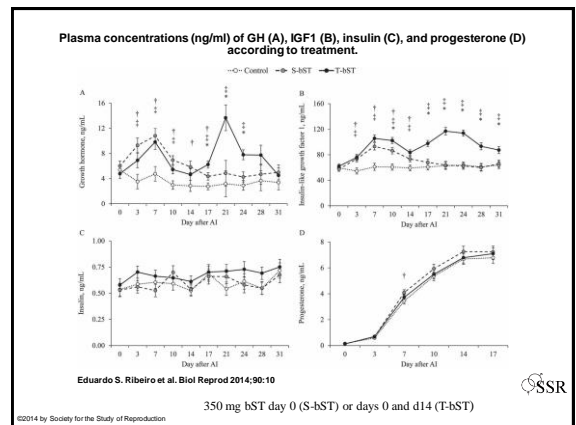
Top up-regulated genes in endometrium according to NEB status

Gene Symbol	Fold Change	Gene Title
MMP1	28.8	matrix metalloproteinase 1
MMP3	14.0	matrix metalloproteinase 3 (stromelysin 1)
MMP13	9.4	matrix metalloproteinase 13 (collagenase 3)
S100A8	9.4	S100 calcium binding protein A8
S100A9	8.3	S100 calcium binding protein A9
S100A12	8.2	S100 calcium binding protein A12
CXCL5	14.8	chemokine (C-X-C motif) ligand 5
BLA-DQB	11.3	MHC class II antigen
IL-1R	8.3	IL-1 receptor
IL8	8.1	interleukin 8
IL8RB	6.4	interleukin 8 receptor, beta
AHSG	8.0	alpha-2-HS-glycoprotein

Wathes et al. (2009) *Physiol. Genomics* 39:1-13



RS Robinson et al. (2000) *J. Endocrinol.* 165: 231-243



Eduardo S. Ribeiro et al. *Biol Reprod* 2014;90:10

350 mg bST day 0 (S-bST) or days 0 and d14 (T-bST)





**Claire Wathes - GH and IGF1 uncoupling; consequences and management**

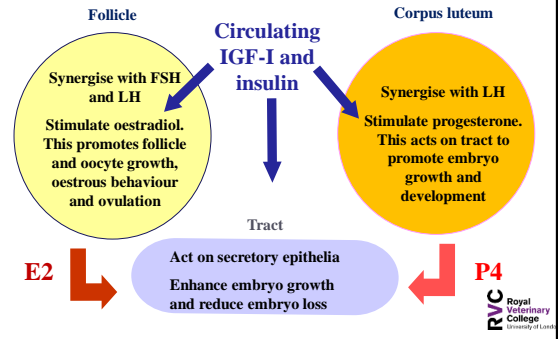
**Ribeiro et al. (2014) Effect of bST on fertility**

Farm	Parameter	CONT	T-bST	P
<b>Herd A (n)</b>				
Jersey	% pregnant d 31	33	41	0.06
8,300 kg/cow	% pregnant d 66	25	35	0.02
	% calved	24	34	0.01
<b>Herd B (n)</b>				
Holstein x Jersey x SR	% pregnant d 31	39	47	0.26
9,000 kg/cow	% pregnant d 66	36	42	0.29
	% calved	30	35	0.34

Synchronised 2 x Estrumate 14 days apart. AI at estrus.  
 2x 325 mg BST days 0 and 14.

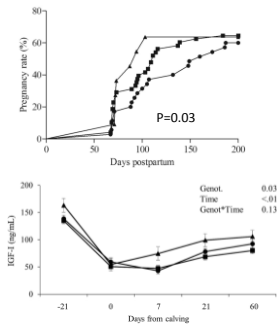
Ribeiro et al. JDS (2014) 90:1-12

**Summary of effects of metabolic hormones on the ovary and reproductive tract**



**Association between growth hormone receptor Alu1 polymorphism and fertility of Holstein cows**

● GHR Alu1 (+/+)   ■ GHR Alu1 (+/-)   ▲ GHR Alu1 (-/-)



**Comparison of somatotrophic axis between Fert+ and Fert- Holstein cows**

Blood samples and liver biopsy taken at -20,+2, +58, +145 and +245 d pp.  
 Fert+, n=11, Fert-, n=12

**Differences**

- Fert+: >circulating IGF1 post- but not pre-calving
- Fert-: >GHR<sub>tot</sub> hepatic mRNA pre-calving
- Fert-: >IGFBP-2, -4, -5 and -6 hepatic mRNA throughout.

**Similarities**

- Milk yield
- BCS
- Circulating insulin
- Hepatic expression of mRNA for IGF1, GHR1A, IGFBP3, AIS, STAT5B, JAK2 or SOCS3

Cummins et al. (2012) JDS 95: 3711-3721

**Summary of metabolic traits associated with long calving to conception intervals**

Time relative to calving	MP cows	PP heifers
-1 week	High leptin, Low NEFA, <b>Low urea</b>	High BCS, <b>High urea</b>
+2 weeks	Low IGF-I, High PMY	
+7 weeks	<b>High urea, High PMY</b>	<b>High urea, BCS loss</b>

DC Wathes et al. (2007). Dom Anim. Endocrinol 33:203-225  
 DC Wathes et al. (2007) JDS 90:1310-1325.



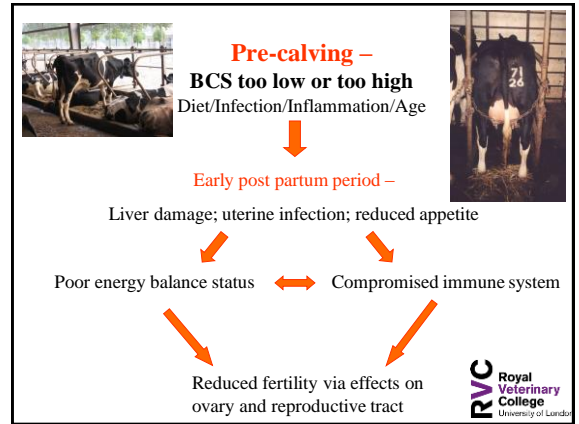
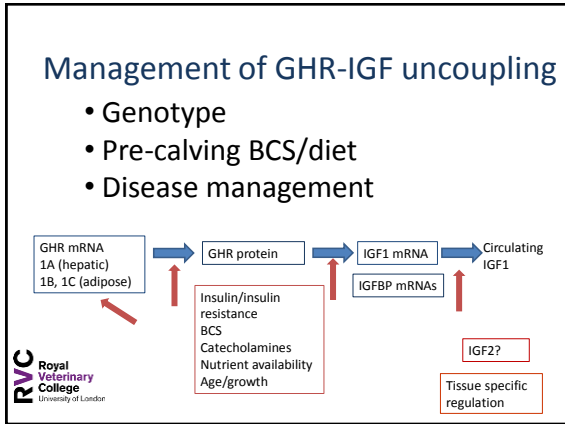
**Metabolic traits associated with failure to conceive**

	Week	Pregnant	FTC	P
MP IGF-I	-1	<b>70 ± 3</b>	54 ± 6	0.03
Urea	-1	<b>4.9 ± 0.2</b>	3.9 ± 0.5	0.07
Urea	+7	<b>5.0 ± 0.2</b>	3.7 ± 0.5	0.02
PP Urea	-1	4.3 ± 0.2	<b>5.2 ± 0.4</b>	0.07

DC Wathes et al. (2007). Dom Anim. Endocrinol 33:203-225  
 DC Wathes et al. (2007) JDS 90:1310-1325.



**Claire Wathes - GH and IGF1 uncoupling; consequences and management**



### Acknowledgements

RVC Royal Veterinary College University of London

Jessica Brickell/Cooke  
 Zhangrui Cheng  
 Mark Fenwick  
 Vicky Taylor  
 Sam Llewellyn

All the co-operating farms and vets

AHDB  
 defra  
 CEDAR  
 bbsrc  
 MERIAL

coqasc  
 Richard Fitzpatrick  
 Dermot Morris  
 John Murphy

Wellcome Trust