Pre-natal maternal effects on offspring lactation performance

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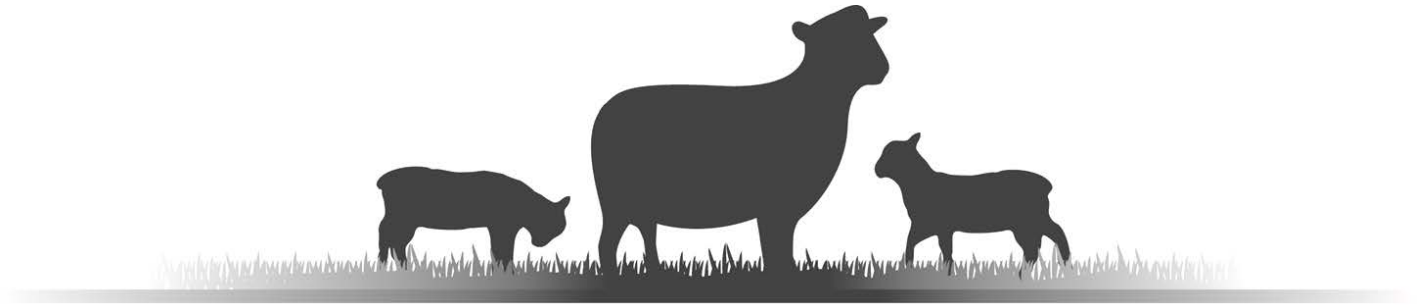

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Foetal programming

- Growing body of evidence demonstrating that manipulation of the maternal environment during gestation can alter foetal development

- “Foetal programming”

Applications for animal production

Our group was interested in how “Foetal Programming” could be applied in an animal production context

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Foetal programming and agriculture

- Firstly; we need evidence that there are actual foetal programming effects in agriculture
- Secondly; if there are effects, are they large enough to have an economic impact?
- Thirdly; can we find the underlying mechanism?
- Fourthly; can we control the effect to consistently achieve the desired outcome?

Our question...

Can the maternal environment affect the lactational performance of the offspring?

Studies designed to investigate the effect of dam nutrition on mammary gland development and milk production of offspring

- Study 1 (2003) Effect of dam gestational nutrition on foetal mammary gland
- Study 2 (2005) Effect of dam size and gestational nutrition on foetal mammary gland and adult offspring lactation performance
- Study 3 (2009) Effect of dam nutrition during early and mid-to-late pregnancy on adult offspring mammary gland and lactation performance

Study 1 (2003) - overview

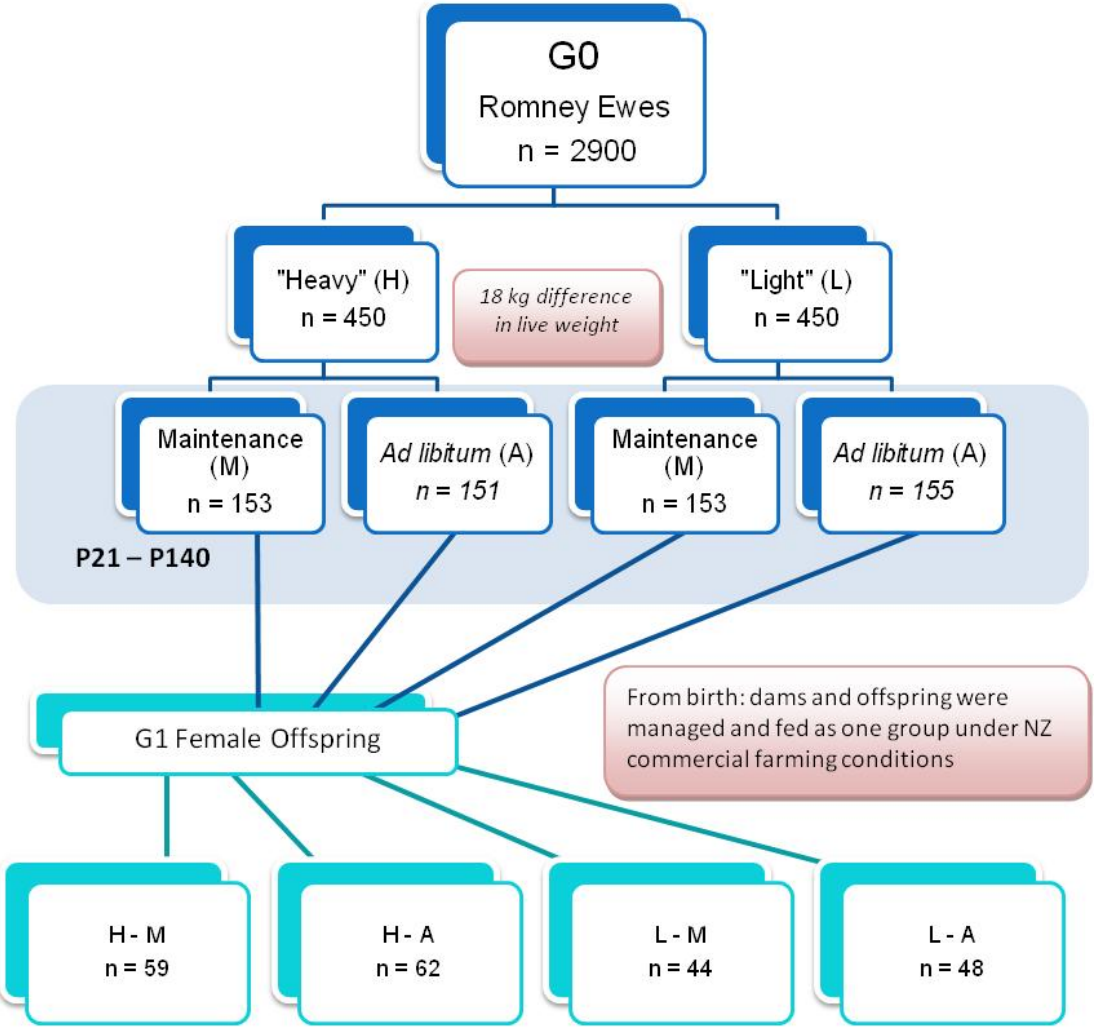
Objective:

To examine effects of maternal nutrition during pregnancy on foetal mammary gland development

Findings: Development of foetal mammary gland affected

- 1.5

Study 2 (2005) – study design



Objectives:

Investigate effects of maternal nutrition during pregnancy on offspring mammary gland development and lactational performance

Additional paradigm of dam size added

van der Linden et al. 2009 J Anim. Sci. 87: 3944-3954
Blair . 2010 J Anim. Sci. 88:E40-E50

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Study 2 - findings

G1 Foetal mammary glands

Dam nutrition affected weight: M > A

Dam size affected duct area: H > L

G1 First lactation performance

Milk yields and composition affected by:

Dam nutrition: M > A

Dam size: H > L

G2 Lamb live weights and growth

Lamb weaning weights affected by:

Dam nutrition: M > A

Dam size: H > L

Do effects persist?

A cohort of lambs was retained to investigate performance traits over 5 years (2007 – 2011)

- Growth
- Reproductive performance
- Lactational performance
- Lambing performance
- Growth performance of 2nd generation offspring

Study 2 – results (5 years)

Ave. LW and BCS over 5 years

Effect of dam size and nutrition on offspring ave. live weight and body condition scores

	Live weight (kg)						Body condition score					
Treatments	Breeding		Late pregnancy		Weaning of lambs		Breeding		Late pregnancy		Weaning of lambs	
Dam nutrition												
M	68.1	0.84	76.6	0.87	64.3	0.72	3.0	0.06	2.3	0.05	2.2	0.04
Ad	70.3	0.90	77.9	0.92	65.4	0.77	2.9	0.06	2.3	0.05	2.1	0.04
value	0.07		0.35		0.31		0.23		0.30		0.30	
Dam size												
Lt	68.6	0.89	76.6	0.89	64.1	0.77	3.0	0.06	2.3	0.05	2.2	0.04
Hv	69.8	0.78	78.3	0.86	66.3	0.73	3.0	0.05	2.3	0.04	2.1	0.04
value	0.30		0.21		0.08		0.51		0.40		0.40	

No significant interaction between dam size and age

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Ave. milk yields over 5 years

Effect of dam size and nutrition on offspring ave. accumulated milk yields (kg milk/42 days)

	Dam Size			Dam nutrition (P21 – 140)		
	Heavy	Light		Maintenance		
2007	114.4 œ2.01	108.4 œ2.60	0.07	115.1 œ2.46[b]	107.7 œ2.24[a]	0.03
2008	102.2 œ2.01	101.0 œ2.41	0.69	99.9 œ2.24	103.3 œ2.52	0.36
2009	124.3 œ3.33	117.7 œ3.45	0.17	119.0 œ3.29	122.7 œ3.55	0.19
2010	109.2 œ3.75	106.4 œ3.48	0.59	105.7 œ3.34	110.7 œ3.70	0.32
2011	138.5 œ3.31	131.0 œ3.90	0.15	134.2 œ3.42	135.7 œ3.42	0.45
All years	117.8 œ1.24[b]	112.6 œ1.39[a]	0.01	114.6 œ1.54	115.5 œ1.35	0.76

No significant interaction between dam size and age in any years

Lambing performance over 5 years

Effect of granddam size and nutrition on grandoffspring ave. live weights

Treatments	Combined lamb LW at birth (kg)		Combined lamb LW at weaning (kg)		Combined lamb LWG birth to weaning (g/day)	
Granddam nutrition						
M	9.7	0.12	55.6	0.51	509.1	5.18
Ad	9.6	0.13	55.2	0.54	506.9	5.48
value	0.29		0.59		0.76	
Granddam size						
Lt	9.6	0.13	54.9	0.55	504.2	5.66
Hv	9.7	0.11	55.9	0.50	511.7	5.07
value	0.63		0.19		0.32	

No significant interaction between dam size and age

Study 2 – summary of findings

- Dam size and nutrition affects development of the foetal mammary gland
- This translates to a milk production difference in 1st lactation
- Effects of dam nutrition do not persist, or lead to long-term production advantage
- Ewes born to heavier dams have increased milk production which persists, but does not result in heavier weaned lambs

Are the effects enough to have an economic advantage?

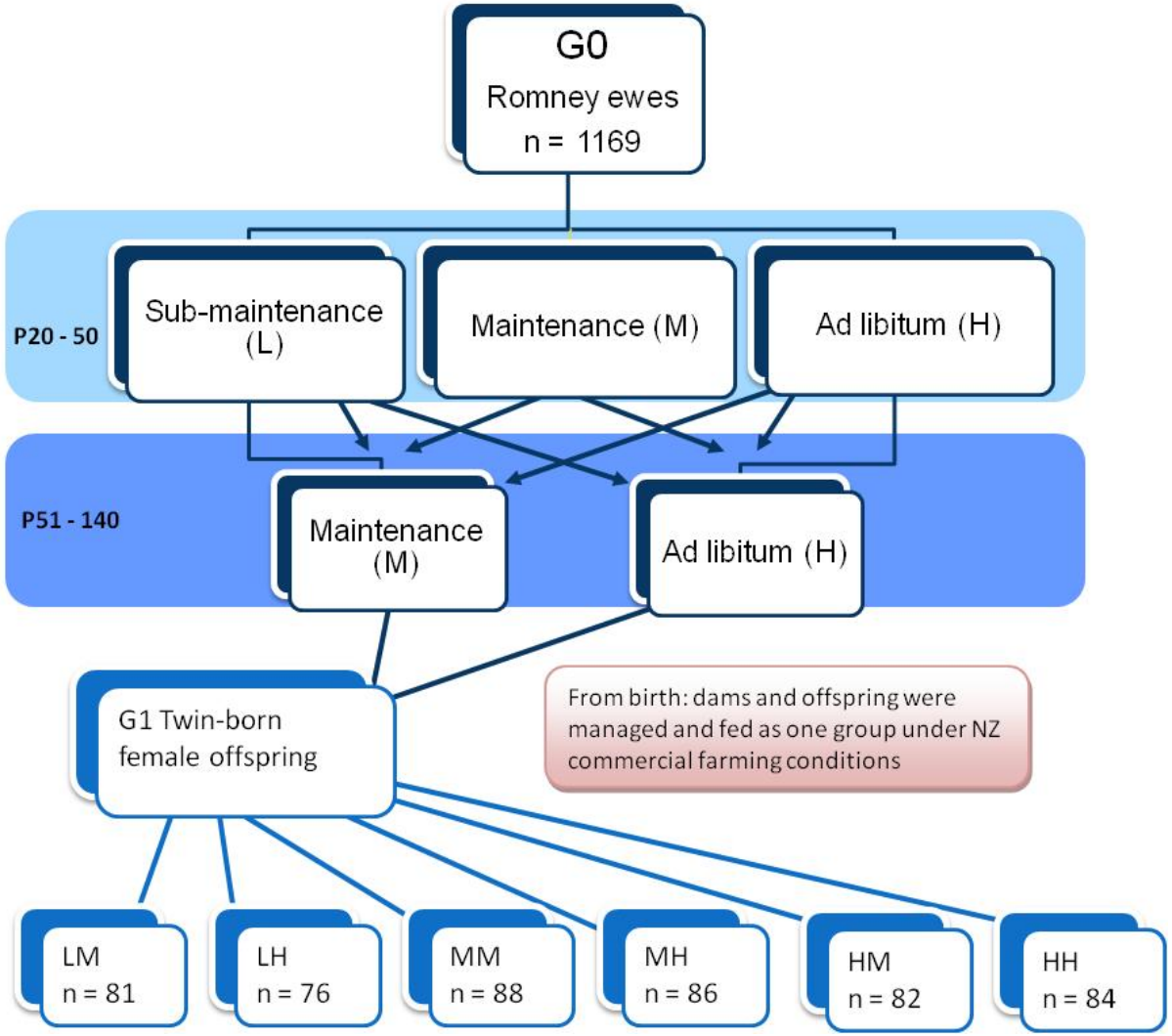
At this stage we would have to suggest not

However:

Can we find the mechanisms underlying 1st lactational differences and manipulate them to achieve a long-term advantage?

Study 3 (current study)...

Study 3 (2009) – study design



- Identify critical programming periods
- Identify optimal maternal feeding conditions
- Identify potential mechanisms

Study 3 - foetal findings

Foetal mammary glands

Weight at foetal D140

- Dam nutrition during P21 – 50: L < M & H
- Dam nutrition during P50 – 140: NS

Suggests early pregnancy as a critical window for programming of the foetal mammary gland from maternal gestational nutrition

Lactational performance

Effect of dam nutrition during early (P21-50) and mid-to-late (P50-140) pregnancy on offspring accumulated milk and components yields (50-d lact. Period) during 1st lactation

	Dam nutrition treatment								
	P21-50					P50-140			
Trait	Sm	M	Ad	SEM	P value	M	Ad	SEM	P value
Milk yield, kg	122.6	133.7	122.5	4.07	0.10	122.3	130.3	3.31	0.10
Lactose yield, kg	6.3	6.9	6.3	0.21	0.12	6.3	6.7	0.17	0.09
CP yield, kg	5.9	6.3	6.0	0.17	0.21	5.9	6.2	0.13	0.19
Fat yield, kg	8.0	9.3	8.6	0.38	0.07	8.5	8.8	0.31	0.42
NE yield, MJ	546.2	613.8	561.8	20.13	0.06	562.1	585.8	16.33	0.32

No significant interaction between dam nutrition during P21-50 and P50-140

Paten . 2013 J Anim. Sci. 91: 676-684

Study 3 - grandoffspring

Effect of granddam nutrition during early (P21-50) and mid-to-late (P50-140) pregnancy on live weight (LW) and growth of grandoffspring from birth to weaning

	Granddam nutrition treatment						
	P21-50				P50-140		
Grandoffspring trait	Sm	M	Ad	SEM	M	Ad	SEM
Birth weight, kg	4.7	4.7	4.7	0.12	4.7	4.7	0.10
LW at weaning, kg	27.3[a]	27.1[ab]	25.2[b]	0.74	26.2	26.8	0.60
Growth rate to weaning, g/d	224.5	221.3	208.5	6.79	213.3	223.0	5.53

No significant interaction between granddam nutrition during P21-50 and P50-140

Paten . 2013 J Anim. Sci. 91: 676-684

Study 3 – summary of findings

- Dam nutrition during early pregnancy is 'critical period'
- Sub-maintenance and ad libitum nutrition detrimental to offspring 1st lactational performance
- Potential intergenerational effect on grandoffspring growth

Study 3 - Mechanisms?

...but what are the underlying mechanisms?

Gene expression differences?

- Mammary gland biopsies of adult ewe offspring
  - Late pregnancy
  - Early-mid lactation

Altered endocrine and/or metabolic profiles?

- Blood serum and plasma collection
  - Late pregnancy
  - Early-mid lactation

Study 3 – Mammary transcriptome

- Many genes involved in milk production
- Examine whole scale gene expression differences in adult offspring mammary gland tissue (biopsied in late pregnancy and lactation)
- RNAseq, RPKM analysis, FDR P value < 0.05, fold difference < 1.5
- Compare gene expression differences between dam early pregnancy nutrition treatments
- Examine molecular pathways

Study 3 – Mammary transcriptome

Late pregnancy	Total no. dif. exp. genes	Gene ontology Of interest
H vs M	45	Replication fork Cell cycle checkpoint Regulation of cell cycle arrest Chromosome (M)
H vs L	16	Cell membrane (H)
M vs L	19	Extracellular (L)
Lactation		
H vs M	1	Galactose metabolism (M)
H vs L	-	-
M vs L	2	Galactose metabolism (M)

Future work – Study 3 +

- Study 3 offspring milked in 2nd lactation – no difference.
- Currently 3rd lactation – additional pregnancy nutrition treatments applied to offspring (milk production)
- Mammary gland and liver biopsies (gene expression)
- Bloods analyses (endocrine and metabolites)
- Histology and immunohistochemistry (cell numbers)
- Currently grandoffspring 1st lactation (milk production)
- Great grandoffspring growth

Summary of studies

- Dam size has lasting effects on offspring milk production but no effect on grand-offspring growth
  - Potential genetic effect – increased feed utilisation efficiency
- Maternal nutrition (particularly during early pregnancy) affects first lactation performance of offspring but does not persist
  - Little difference in LW and BCS
  - Mammogenesis in late pregnancy appears to be affected (secretory cell number)
  - Possibly also cell activity in lactation

Acknowledgments

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Ave. milk composition yields

Effect of dam size and nutrition on offspring ave. accumulated lactose yields (kg)

	Dam size			Dam nutrition (P21 – 140)		
	Heavy	Light		Maintenance		
2007	6.0 œ0.11	5.7 œ0.14	0.03	6.1 œ0.13	5.6 œ0.17	0.01
2008	5.3 œ0.11	5.3 œ0.13	0.75	5.2 œ0.12	5.4 œ0.14	0.26
2009	6.7 œ0.18	6.3 œ0.19	0.13	6.3 œ0.21	6.7 œ0.22	0.22
2010	5.7 œ0.23	5.4 œ0.21	0.39	5.4 œ0.22	5.7 œ0.25	0.45
2011	7.3 œ0.18	6.9 œ0.21	0.16	7.0 œ0.21	7.2 œ0.22	0.60
All years	6.2 œ0.08[b]	5.9 œ0.09[a]	0.01	6.0 œ0.08	6.0 œ0.09	0.95

No significant interaction between dam size and age in any years

Ave. milk composition yields

Effect of dam size and nutrition on offspring ave. Accumulated milk composition yields

	Milk components									
Treatments	CPY, kg		TPY, kg		CY, kg		FY, kg		NEY, MJ	
Dam nutrition										
M	5.7	0.08	5.2	0.07	4.5	0.06	8.2	0.15	539.2	7.81
Ad	5.6	0.08	5.2	0.08	4.5	0.06	8.3	0.16	540.0	8.28
value	0.64		0.63		0.66		0.87		0.94	
Dam size										
Lt	5.5	0.08[a]	5.1	0.07	4.4	0.06	8.2	0.16	535.3	8.12
Hv	5.7	0.07[b]	5.3	0.07	4.6	0.06	8.2	0.14	543.9	724
value	0.04		0.06		0.06		0.98		0.43	

No significant interaction between dam size and age