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WHAT CAUSES THE NEGATIVE GENETIC CORRELATION BETWEEN MATERNAL AND DIRECT EFFECTS FOR LAMB BIRTH WEIGHT?

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SUMMARY

An antagonistic genetic relationship between direct and maternal effects for birth weight (and weaning weight) makes the concurrent genetic improvement of the two traits more challenging than if the correlation was zero or favourable. The direction and magnitude of the genetic correlation between maternal and direct effects for lamb birth weight are equivocal with several moderate negative and several near zero estimates being reported. A number of experiments over the last decade undertaken at Massey University in the pursuit of developmental programming effects in sheep, have provided serendipitous results that suggest a negative phenotypic correlation between dam and offspring birth weight can be induced by some environmental stressors during pregnancy. These correlations could be interpreted as having an underlying genetic effect, since the relationship is generated without any experimental manipulation of second generation lambs. It is proposed that mining existing datasets might be a fertile ground to conduct research for further exploration of this possible explanation of the negative genetic correlation between direct – maternal effects for birth weight.

INTRODUCTION

The dam – fetal conflict has long been recognised in both domestic animals and humans. A series of papers in the Journal of Animal Science in 1972 reviewed maternal and direct genetic effects in various species and also reviewed techniques for estimating the effects; Bradford (1972) is particularly relevant to this paper. Haig (1993) published a seminal paper entitled "genetic conflicts in human pregnancy" which advanced thinking about the biology of human pregnancy. Haig's contribution has become encapsulated in the phrase "Haig's conflict", which describes the need for dams to control the resources that a foetus demands from its mother. At a similar time Hales and Barker (1992) proposed the thrifty phenotype (also known as the Barker hypothesis) to explain a putative effect of events during pregnancy on new-born and adult phenotypes.

An important feature of the dam – fetal relationship is that many estimates of maternal – direct correlations for both birth weight (and weaning weight – not discussed further) are negative (Table 1; see also reviews by Gootwine *et al*. 2007 and Brien *et al*. 2014). This is suggestive of an evolutionary effect that may avoid risk to the dam of gestating a large foetus that cannot easily pass through the birth canal and/or minimises the opportunity for a species to outgrow its ecological niche by continuing to increase in body size over time. Female mammals with low fecundity must successfully reproduce at least 3 times to maintain population size and therefore they cannot afford to invest all their bodily resources in the current foetus. However, the neonate is often born into a dangerous environment and they want to be large and healthy with energy reserves and therefore it has a drive to scavenge resources.

Since the late 1990s, there has been a growing interest in developmental programming and the likely epigenetic mechanisms (Langley-Evans 2006). While the various epigenetic mechanisms (methylation, acetylation, small RNA's) are now accepted, there is still much to learn about their roles in intra- and inter-generational effects on animal phenotypes. The phenotypic effects of maternal and paternal imprinting (involving epigenetic mechanisms) have also been recognised in production animals, and it is possible that imprinting contributes to quantitative variation in production traits (Wolf *et al.* 2008).

The purpose of this paper is to report on some serendipitous results for lamb birth weight obtained from a series of experiments designed to identify possible developmental programming effects. One possible explanation of the results is an epigenetic effect for either maternal or direct effects on birth weight.

METHODS

Sheep experiments were undertaken at Massey University from 2005 to 2014 in which birth weights were collected for 2 generations. The first generation (G1) were born to dams which were either exposed to differential feeding during pregnancy (Kenyon *et al.* 2011, Paten *et al.* 2011) or whose dams differed in age (Loureiro *et al.* 2012). Female offspring (G2) were retained, treated as one group and the birth weight of their offspring recorded.

G1 birth weight data were analysed using PROC GLM in SAS with a linear model that included the effects of dam treatment (level of pregnancy feeding or dam age), lamb sex and lamb birth rank and a covariate for date of birth. G2 birth weights were analysed in a similar manner except the treatment effect was that of their grand-dams.

Table 1. Heritability estimates for direct lamb birth weight, maternal effect and the genetic correlation between maternal and direct effects

Author	Maternal	Direct	Correlation
Tosh and Kemp (1994)	0.13 to 0.31	0.07 to 0.39	-0.13 to -0.56
Nasholm and Danell (1996)	0.30	0.07	+0.11
Larsgard and Olesen (1998)	0.42	0.22	-0.10
Yazdi *et al.* (1999)	0.14	0.15	+0.10
Ligda *et al*. (2000)	0.19	0.18	-0.44
Al-Shorepy (2001)	0.33	0.42	-0.60
El Fadili and Leroy (2001)	0.28	0.01	+0.01
Ekiz *et al*. (2004)	0.10 to 0.27	0.09 to 0.33	-0.48 to -0.55
Oliveira Lôbo *et al*. (2009)	0.18	0.42	-0.47
Prince *et al*. (2010)	0.08 to 0.34	0.14 to 0.28	-0.48 to -0.57

RESULTS AND DISCUSSION

In the first experiment where ewes were differentially fed during pregnancy (Kenyon *et al.* 2011), there was an interaction between feeding treatment and birth rank for birth weight such that only G1 twins were affected, with those from restricted-fed dams being lighter (Table 2). In all 4 years of G2 birth weight data (ewes aged 2 to 5 year-old), ewes from restricted-fed dams gave birth to heavier lambs than the ewes from a*d lib*-fed dams. In the second differential feeding experiment (Paten *et al.* 2011), restricted feeding during pregnancy did not decrease G1 birth weight and there were no effects of grand-dam feeding on G2 birth weights (data not shown).

It was unsurprising that the G1 birth weights of lambs born to one-year-old ewes were substantially lighter than lambs born to mature dams (Loureiro *et al.* 2012). Indeed, twin lambs born to one-year-old dams were on average 1.5kg lighter than singleton lambs born to mature dams (3.4±0.14kg versus 4.9±0.18kg). This live weight handicap persisted into maturity with G1 1½ year-old ewes being nearly 10kg lighter than their singleton born counterparts (55.9±1.01kg versus 65.2±1.30kg). However, what was surprising was that these lighter G1 ewes gave birth to heavier G2 lambs in their first three lambings (Table 2).

The above results suggest that the birth weights of lambs born to the stressed dams are often lighter than those from non-stressed dams. However, exceptions did occur, whereby singletons

born in the first differential pregnancy feeding experiment did not have modified birth weight according to their dams pregnancy feeding and also in the second differential feeding trial where differences in birth weight did not eventuate. Similar variable results are commonplace in the literature.

In second generation animals, there is a surprising effect whereby ewes which were born small due to a stress on their dam during pregnancy, themselves go on to give birth to heavier lambs. There are few reports from similar experiments in the literature. Contrary to the above observation, Gardiner *et al.* (2007) reported that lamb birth weight increased by 149g for every 1kg increase in the dam's own birth weight. However, their study did not entail any systematic manipulation of the pregnant dam. Furthermore, analyses considering singleton versus twin born ewes do not show that twin-born ewes produce heavier lambs. These inconsistent outcomes suggest there is some, as yet unexplained, biological phenomenon that occasionally results in the reversal of light birth weight between generations. The challenge is to understand the biological mechanisms that underpin the dam-foetus relationship so that it might be manipulated.

Based on the results presented here it might be worthwhile for those analysing the association between direct and maternal effects to reconsider how the relationship is construed both in biological and biometrical terms. A typical analysis assumes only genetic and environmental effects, whereas it is possible there could be epigenetic effects acting on birth weight via either the direct growth genes or the maternal uterine genes. Geoghegan and Spencer (2013) proposed a simple model that could be developed to examine epigenetic effects, while Goddard and Whitelaw (2014) suggested that it might not be necessary to change the way in which animal genetic merit is predicted in the presence of epigenetic effects. However, when there are two traits in a selection objective that are apparently antagonistically genetically correlated, genetic gain in each of those traits will be less than when compared to a situation where the traits are favourably correlated. The question then arises as to whether a seemingly antagonistic genetic correlation that is caused by an epigenetic effect can either be accounted for or ignored (r_g set to 0).

Table 2. Lamb birth weights of dams which were either differentially feed during pregnancy or were of different ages (G1) and the birth weights of their offspring (G2)

Dam treatment	G1 birth weight (kg)	G2 birth weight (kg)			
Pregnancy feeding		2007	2008	2009	2010
Ad lib	6.0 (single)				
	5.1 (twin)	4.3	4.5	4.8	5.0
Restricted	5.9 (single)				
	4.6 (twin)	4.7	4.8	5.2	5.2
Std error	0.07	0.10	0.10	0.11	0.11
Dam age		2011	2012	2013	
Mature	4.6	5.1	5.1	5.7	
One-year-old	3.7	5.6	5.7	6.0	
Std error	0.15	0.11	0.09	0.13	

Various commentators have noted that much research effort is being devoted to exploring epigenetic effects. However, repeatable farm animal paradigms are sparse in the literature, experimental costs are significant and experiments take years to complete (Kenyon and Blair 2014). As a first step, it might be worthwhile to mine datasets used to estimate genetic parameters, although in the absence of a systematic manipulation of the dam during pregnancy to induce a

significant change in birth weight, it may be difficult to detect swings in birth weight such as those reported in Table 2. It would seem worthwhile for those with quantitative animal breeding and genetics skills to brainstorm with those having interests in epigenetic mechanisms to examine whether current models of some quantitatively inherited traits need to be reconfigured. If the biological mechanisms underlying the apparent negative genetic correlation between maternal and direct effects for birth weight (and weaning weight) can be untangled it may be possible to directly manipulate the mechanisms to benefit animal growth and consequently farm profit.

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