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BRIEF COMMUNICATION: Developmental programming in sheep due to early pregnancy nutrition alters milk yields of adult female offspring but not of grand-offspring

SW Peterson*, SJ Pain, CMC Jenkinson, PR Kenyon and HT Blair

Institute of Veterinary, Animal and Biomedical Sciences, Massey University, Private Bag 11-222, Palmerston North 4442, New Zealand.
**Corresponding author. Email: s.peterson@massey.ac.nz*

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Introduction

Two long-term studies by our group have shown that nutrition of the pregnant dam altered the growth and development of the ewe offspring, and their subsequent lactational performance (van der Linden et al. 2009; Paten et al. 2013a). These effects were attributed to developmental programming possibly via epigenetic changes. Epigenetic regulation, such as histone modifications and chromatin condensation, has been implicated in the short- and long-term control of transcription in mammary epithelial cells (Kress et al. 2010).

In the first long-term trial, ewe offspring (G1) born to dams (G0) fed pasture to maintenance requirements during pregnancy (days 21 to 140 of gestation) produced greater milk, lactose and crude protein yields in their first lactation than did ewes born to dams fed *ad libitum* (van der Linden et al. 2009). These ewes were monitored over five lactations and the differences evident in the first lactation were not apparent in subsequent lactations (Paten et al. 2013b). It was hypothesised that the *in utero* programming effects had been either removed or reprogrammed during mammary gland involution and regrowth for subsequent lactations.

To investigate the possibility that the developmental effects had been passed onto the grand-offspring, (i.e., transgenerational; Riggs et al. 1996) G2 ewe offspring, born at the second parity of the G1 ewes, were milked at their first lactation. However, the lactational performance of these first-parity grand-offspring (G2) was not affected by nutritional treatments applied to their grand-dams (G0) during pregnancy (Peterson et al. 2012).

Similarly, the second long-term trial investigated the effect of maternal nutrition during pregnancy on the milk yield of adult daughters, but the design differed slightly. Instead of applying the same nutritional treatment from day 21-140 of gestation, dams (G0) were fed one of three feeding treatments (low, medium or high) in early pregnancy (days 21-50) and one of two feeding treatments in mid-to-late pregnancy (days 50–140) (Kenyon et al. 2011). Ewes born to dams allowed a medium pasture DM intake in early pregnancy tended to have greater accumulated milk, fat and net energy (NE) yields in a 50-d lactation compared with G1 ewes born to dams fed sub-maintenance or *ad libitum* during early pregnancy. In contrast, G1 ewes born to dams allowed *ad libitum* food intake during mid-to-late pregnancy tended to have greater accumulated milk and lactose yields compared with G1 ewes born to dams allowed only a medium pasture DM intake. As in the first trial, lactational performance of G1 offspring was altered only in their first lactation (Blair et al, 2010; Paten et al. 2013a). In all trials, only twin-rearing ewes were milked.

In the first trial, G2 ewes born to the second parity of G1 ewes were milked, but not those born to the first parity. There was no significant effect of grand-dam nutritional treatment on lactational performance (Peterson et al. 2012). Subsequently, it was hypothesised that the programmed signal might have been lost during the first lactation of the G1 ewes, and so, their second-parity daughters were not affected. However, it is possible that the first-parity daughters may have retained the (transgenerational) developmental programming signal and this was tested in the G2 ewes born in the second long-term trial.

The study reported here investigated possible long-term intergenerational effects of G0 pregnancy nutrition on first-lactation milk yield of grand-offspring (G2) born to first-parity G1 ewes.

Materials and Methods

Background

The ewes in the present study (G2) were born in 2011 from G1 ewes whose dams (G0) had been fed one of three feeding treatments in early pregnancy and one of two feeding treatments in mid-to-late pregnancy (Kenyon et al. 2011). Briefly, at day 21 of pregnancy, ewes were allocated to either sub-maintenance (SM), maintenance (M) or *ad-libitum* (Ad) feeding until day 50 of pregnancy, at which time they were randomly reallocated to either M or Ad feeding levels to day 140 of pregnancy. For the remainder of their lives they were managed under commercial conditions. During days 21 to 50 of pregnancy total liveweight changes of the SM, M and Ad groups were -0.15 ± 0.02, -0.02 ± 0.02 and 0.15 ± 0.02 kg/d respectively, and between days 50 and 140 of gestation total liveweight gains of 0.119 ± 0.01 and 0.260 ± 0.01 kg/d were achieved in the M and Ad groups respectively (Kenyon et al. 2011b).

Experimental design and animals in present study

The present study utilised 52 two-year-old G2 Romney ewes, which had been mated to Romney rams following synchronisation with progesterone-containing controlled-internal-drug-release devices (CIDR, 0.3 g progesterone, Ezi-Breed CIDR, Pfizer Animal Health Ltd, Auckland, New Zealand). Subsequently, all ewes were maintained under commercial farming conditions at Massey University's Keeble Farm, Palmerston North, New Zealand. This study was conducted with approval of the Massey University Animal Ethics Committee.

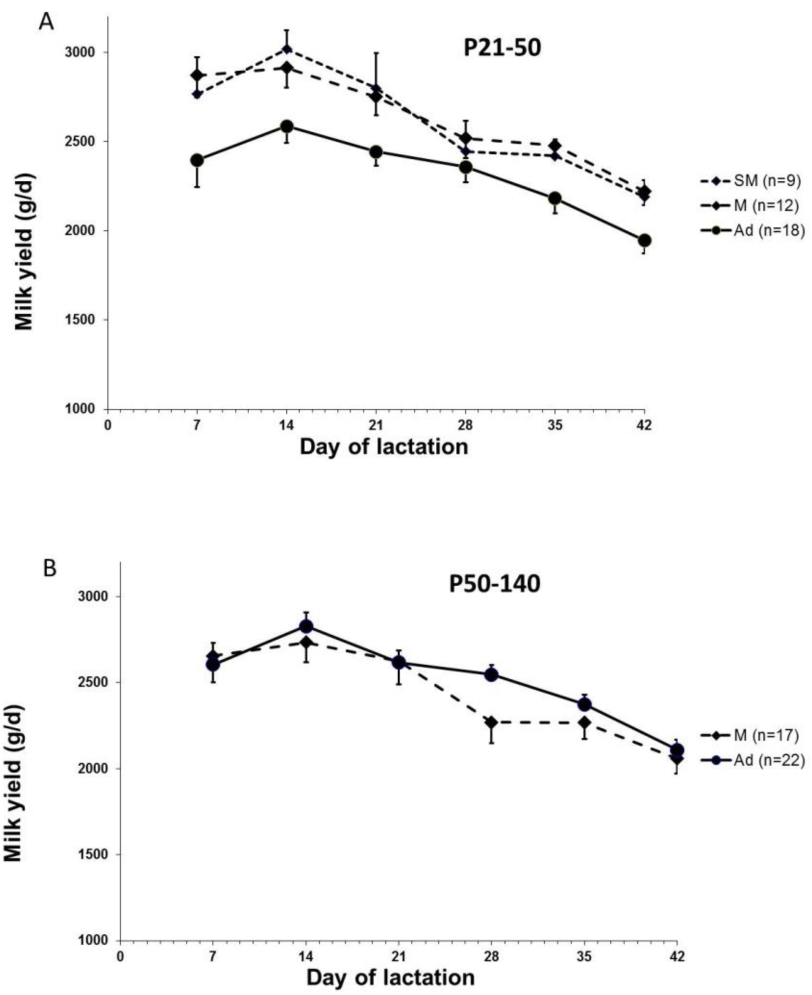
Ewes were enrolled in the trial if they lambed during the first or second cycle and if they gave birth to twins, and were excluded from the trial if one lamb died or if they contracted clinical mastitis. Numbers of G2 ewes finally included in the analyses from each G0 treatment group were: SMM (n = 6), MM (n = 11), AdM (n = 9), SMAd (n = 6), MAd (n=9) and AdAd (n=11).

Ewes were milked one day a week starting 7 ± 1 days after lambing and continuing for six weeks in total. Milk yield of the ewes was estimated by the 'oxytocin method' first described by McCance and Alexander (1959). The technique involves i.v. injection of 1 i.u. synthetic oxytocin then emptying the udder by machine and hand milking, and repeating the milking procedure a known time (about 6 h) later, at which time the milk yield is measured. The lambs were separated from the ewes (and bottle-fed as required) during the intervening period whilst the ewes returned to pasture.

Statistical analysis

Data were analysed using the computer statistical package REG (Gilmour 1990). Multivariate (repeated-measures) analysis of variance was used to analyse all time-series data. Orthogonal contrasts were used to compare milk yields of treatment groups within the early gestation period. Postpartum live weight of G2 ewes significantly affected milk yield and remained in the statistical models; cycle of mating/birth was not significant and was removed from models.

Figure 1 First-lactation milk yields of (twin-bearing) grand-offspring (G2) of (G0) ewes fed at pasture to sub-maintenance (SM), maintenance (M) or *ad-libitum* (Ad) intake during early pregnancy (P21-50) (graph A), and either M or Ad intake from P50-140 (graph B).



Results and discussion

Ewe live weight did not differ among treatment groups (data not shown). Milk yields of G2 ewes were not significantly affected by the nutrition of their grand dams, during early gestation (Figure 1 A) nor during late gestation (Figure 1 B). Previously we have examined the milk yield of second-parity G2 ewes whose grand dams were fed differentially during gestation and also found no treatment effect (Peterson et al. 2012), but we had hypothesised that any potential effects of fetal programming may have been abolished during the first lactation of their G1 dams. The current results, combined with our earlier study, indicate that programming of the fetal mammary gland does not transfer to the next generation. This is consistent with the hypothesis that the mammary gland is pliable and may be reprogrammed at certain times by various environmental influences through, for example, acute DNA methylation regulating gene expression in mammary epithelial cells (Singh et al. 2012). Thus, because epigenetic mechanisms in the mammary gland are labile, they have not passed to the granddaughters.

Although epigenetic effects were defined, some years ago, as “stable alterations of gene expression through DNA methylation and histone modifications of the fetal genome” (Wu et al. 2007) capable of surviving rounds of cell division and even transgenerational transfer (Riggs et al. 1996), and it is accepted that epigenetic marks are generally maintained for the life of an organism (Singh et al. 2012), we must now consider that mammary tissue continues to be sensitive to environmental signals that can alter acute programming of gene expression.

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