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## Effects of maternal nutrition during pregnancy on the growth and reproductive development of male sheep: a meta-analysis

K Asmad<sup>a\*</sup>, S Nakagawa<sup>b</sup>, N Lopez-Villalobos<sup>a</sup>, PR Kenyon<sup>a</sup>, SJ Pain<sup>a</sup> and HT Blair<sup>a</sup>

<sup>a</sup>*Institute of Veterinary, Animal and Biomedical Sciences, Massey University, Private Bag 11-222, Palmerston North 4442, New Zealand;* <sup>b</sup>*Department of Zoology, University of Otago, PO Box 56, Dunedin 9016, New Zealand*  
*\*Corresponding author. Email: a.kari@massey.ac.nz*

### Abstract

Nutrient supply to the fetus is one of the crucial factors in the regulation of fetal growth and reproductive development. The effect of maternal nutrition can be exerted at all stages of fetal development, from conception until birth. A meta-analysis of maternal nutrition effects on the growth and reproductive development of male sheep offspring was undertaken using sixteen sheep studies. Eleven studies were included for prediction of the growth curves using a logistic growth model, and eleven studies were included for reproductive development and analysed using a mixed model. The meta-analysis suggested that, male sheep offspring undernourished during gestation had a significantly slower growth and lower testosterone levels while there were no statistically significant effects on testis weight, seminiferous tubule diameter or Sertoli cell count. The lack of a statistical effect on seminiferous tubule diameter and Sertoli cell count may be due to the limited number of studies examining the effects of maternal nutrition during pregnancy on male sheep offspring reproductive development. The meta-analysis reported here suggests that additional studies are warranted to more conclusively determine whether maternal nutrition during pregnancy effects male sheep growth and reproductive development.

**Keywords:** meta-analysis; maternal nutrition; growth; reproductive traits; male offspring

### Introduction

In animal production systems of temperate countries, sheep are pregnant throughout winter when feed is limited in availability. This creates a situation where maternal feeding level may not be optimal. However, prenatal nutrition is one of the crucial factors regulating fetal growth (Lumey 1992) and development of the fetal reproductive system (Rhind 2004). Evidence from previous studies also indicated that maternal undernutrition altered weight, testicular development and hormonal regulation in male offspring (Bielli et al. 2001; Da Silva et al. 2001; Rae et al. 2002b).

During the prenatal period, there are a number of critical phases of fetal reproductive development. For example, in sheep, testicular differentiation occurs around Day 27 of gestation followed by steroidogenesis and the activation of associated enzyme systems (Rhind 2004). Sertoli cells are present at around Day 34 of gestation, seminiferous cords between Day 35 to 40 (Sweeney et al. 1997; Rhind et al. 2001), and Leydig cells from Day 42 (Hochchereau-de Reviers et al. 1995). Sertoli cell replication continues throughout fetal life and after birth with maximum numbers reached before 40 to 80 days of postnatal age (Hochchereau-de Reviers et al. 1987). By Day 70 of gestation, the rete testis is organised in the centre of testis (Sweeney et al. 1997) and between Days 35 and 85 of gestation the GnRH neuronal system develops in the hypothalamus (Caldani et al. 1995). Therefore, development of the

male's reproductive system is almost complete by birth, except for the Sertoli cells.

Generally, pregnancy is divided into three trimesters. Gunn et al. (1995) and Rhind et al. (1998) showed that nutrition during the first and last trimesters of pregnancy are crucial for fetal development. During the first trimester of pregnancy, the energy requirements for fetal development are relatively small but fetal metabolic activity is high. During the last trimester of pregnancy, fetal growth is maximum and associated with the highest nutritional demand. Ehrhardt & Bell (1995) showed that, in sheep, placental growth is completed before Day 100 of pregnancy when the developing fetus was approximately 25% of its final birth weight (Robinson et al. 1977).

There have been a number of studies in sheep examining the effect of maternal nutrition during gestation on growth and reproductive development, but the results have not been consistent. Meta-analysis relies on effect size using a scale free indicator of the intervention effect to quantitatively construct overall conclusions where data on the magnitude of the effect may be derived from the literature (Cohen 1988). It is hypothesised that restricted maternal nutrition during gestation affects the growth and reproductive development of male offspring. To test this hypothesis, sixteen sheep studies were reviewed and meta-analyses undertaken to examine the effect of maternal nutrition restriction on the growth and reproductive development of male sheep offspring.

**Table 1** Summary of references used in the meta-analysis for determining the effect of maternal nutrition regimen and timing of nutritional regimen on the growth of male sheep offspring.

Nutritional treatment	Days post conception during which nutritional treatment imposed	Effect on Restricted group	Reference
Control group (Improved pasture + grain supplement) or Treated group (Native pasture).	1–99	Reduced birth weight and live weight at 99 days of age ( $P < 0.01$ ).	Bielli et al. (2001)
High ( <i>Ad libitum</i> ) or Moderate (to allow liveweight gain of approximately 75 g/day).	1–145	Increased fetal weight ( $P < 0.001$ ).	Da Silva et al. (2001)
High (100% ME) or Low (50% ME).	1–145	No differences in birth weight and live weight at 20 months of age.	Rae et al. (2002a)
High (100% ME) or Low (50% ME).	1–30, 31–50, 1–50, 1–30, 31–65, 1–65, 1–30, 31–65, 65–110, 1–110	No differences in fetal weight.	Rae et al. (2002b)
Control (100% protein intake) or Restricted (50% protein intake).	1–119	No differences in fetal weight.	Rae et al. (2002c)
High ( <i>Ad libitum</i> ) or Moderate (to allow liveweight gain of approximately 75 g/day).	1–103	No differences in male fetal weight.	Da Silva et al. (2003)
High ( <i>Ad libitum</i> ) or Maintenance (to ensure no change in total live weight).	21–140	No differences in fetal weight and live weight.	Kenyon et al. (2009)
Control (100% ME) or Restricted (50% ME).	1–30, 31–100	No differences in live weight.	Kotsampasi et al. (2009)
Control (100% ME) or Restricted (50% ME).	1–30, 31–100	No differences in birth weight and live weight.	Simitzis et al. (2009)
Control (110% ME) or Restricted (70% ME).	110–145	No differences in birth weight.	Smith et al. (2010)
Control ( <i>Ad libitum</i> ) or Maintenance (to ensure no change in total live weight) or Sub-Maintenance (to achieve a loss in total live weight of 100 g/d).	21–50, 50–140	No differences in fetal weight and live weight.	Kenyon et al. (2011)

## Materials and methods

### Literature search

A systematic search was undertaken using ‘PubMed’ and ‘Web of Science’ databases, reviews, and reference lists of relevant papers. The search strategy employed keywords of maternal nutrition or maternal diet and male growth or male reproduction and trial without language and time limitation. Sixteen sheep studies were identified for this meta-analysis. Eleven studies were included for prediction of growth curves, and eleven studies were included to examine reproductive development.

### Study selection

Studies were eligible for inclusion if they included a control or comparison group level of maternal nutrition during pregnancy and measured the growth or reproductive development of sheep male offspring.

The details of studies included in the meta-analysis for predicting growth curves are summarised in Table 1 and for examining reproductive development in Table 2. The maternal nutritional regimen, the specific periods of treatment and the growth and reproductive development of male sheep offspring are included in the tables.

### Data extraction

A total of 16 studies with growth and reproductive development data met the eligibility criteria for meta-analysis. The recorded data included the journal/year of publication, country and author, duration of feeding restriction, number and age of sheep for Control (*ad libitum* intake) and Restricted feeding groups offered less than *ad libitum* intake, mean values related to growth as measured by fetal weight, birth weight and live weight, and mean values related to reproductive development as measured by individual testis weight, plasma testosterone level,

**Table 2** Summary of references used in the meta-analysis for determining the effect of maternal nutrition regimen and timing of nutritional regimen on the reproductive development of male sheep offspring.

Nutritional treatment	Days post conception during which nutritional treatment imposed	Effect on Restricted group	Reference
High (110% ME) or Low (90% ME)	30–146	No differences in testis weight.	Deligeorgis et al. (1996)
Control group (Improved pasture + grain supplement) or Treated group (Native pasture)	1–99	Reduced left and right testis weight ( $P < 0.001$ ), seminiferous tubule diameter ( $P < 0.01$ ) and number of Leydig cells ( $P < 0.001$ ); no differences in number of Sertoli cells.	Bielli et al. (2001)
High ( <i>Ad libitum</i> ) or Moderate (to allow liveweight gain of approximately 75 g/day)	1–145	Reduced testosterone concentration ( $P < 0.05$ ).	Da Silva et al. (2001)
High (110% ME) or Low (70% ME)	70–145	Increased number of Sertoli cells ( $P < 0.03$ ), and no differences in testicular weight (left, right or paired), and seminiferous tubule diameter.	Bielli et al. (2002)
High (100% ME) or Low (70% ME)	22–90, 22–135	No differences in testis weight at Day 90 and Day 135 of gestation.	Osgerby et al. (2002)
High (100% ME) or Low (50% ME)	1–145	No differences in scrotal circumference and number of spermatozoa.	Rae et al. (2002a)
High (100% ME) or Low (50% ME)	1–30, 31–50, 1–50, 31–65, 1–65, 65–110, 1–110	Increased and decreased in testosterone concentration ( $P < 0.05$ ) and no differences in fetal testicular weight.	Rae et al. (2002b)
Control (100% protein intake) or Restricted (50% protein intake)	1–119	No differences in testis weight.	Rae et al. (2002c)
High ( <i>Ad libitum</i> ) or Moderate (to allow liveweight gain of approximately 75 g/day)	1–103	No significant differences in fetal testicular weight, number of seminiferous cords and Sertoli cells count.	Da Silva et al. (2003)
High ( <i>Ad libitum</i> ) or Maintenance (to ensure no change in total live weight)	21–140	No differences in testis weight.	Kenyon et al. (2009)
Control (100% ME) or Restricted (50% ME)	1–30, 31–100	Reduced number of Sertoli cells ( $P < 0.01$ ), seminiferous diameter ( $P < 0.05$ ), no differences in testosterone levels and testis weight.	Kotsampasi et al. (2009)
Control ( <i>Ad libitum</i> ) or Maintenance (to ensure no change in total live weight) or Sub-Maintenance (to achieve a loss in total live weight of 100 g/d)	21–50, 50–140	No differences in testis weight.	Kenyon et al. (2011)
Control ( <i>Ad libitum</i> ) or Maintenance (to ensure no change in total live weight) or Sub-Maintenance (to achieve a loss in total live weight of 100 g/d)	21–50, 50–140	No differences in testis weight.	Martin (2011)

seminiferous tubule diameter and Sertoli cell count of male sheep offspring. The age of the male offspring used in the studies from which the data for meta-analysis were collected ranged from a minimum of 30 days gestation to 301 post-natal days of age.

### Statistical analysis

Statistical analyses were carried out using SAS (2008) for analysis of variance. Growth data were analysed in two steps. Firstly, growth curves were

modeled using the NLMIXED procedure to obtain random regression coefficients for a group of animals in the Control and Restricted treatments in each study using the following logistic growth model:

$$W_t = A / (1 + B^{-Ct})$$

where  $W_t$  is the weight at age  $t$ ,  $A$  is the asymptotic live weight and  $B$  and  $C$  are model parameters that characterise the shape of the curve.

Secondly, predicted values of live weight at 50-day intervals after conception were predicted for each

treatment and study, and analysed using the MIXED procedure with a linear model that included the fixed effect of treatment, age in days and the interaction of treatment and age plus the random effect of study. Means and standard errors were obtained for each treatment and age.

Reproductive variables involving testis weight, seminiferous tubule diameter and Sertoli cell count, were analysed after  $\log_{10}$  transformation using the MIXED procedure with a mixed model including fixed effect of treatment, age as a covariate and study as a random effect. Predicted means and their standard errors for each treatment were obtained from the mixed models. Testosterone level was analysed using the Proc GLIMMIX procedure with a model including treatment as a fixed effect, age as a covariate and study as a random effect. The distribution of data to follow a Poisson distribution and log transformation was used as a link function. Comparison between means was compared using the Tukey adjustment.

In meta-analytic studies, effect size statistics such as standardized mean difference (Hedge's  $g$  or Hedge's  $d$  for small sample sizes) are used to compare effects.

Hedge's  $g$  was calculated as:

$$\text{Hedge's } g = (m_1 - m_2) / \sqrt{((n_2 - 1) s_2^2 + (n_1 - 1) s_1^2) / (n_1 + n_2 - 2)} \quad (\text{Hedges \& Olkin 1985})$$

where  $m$  = the mean of each treatment group in the trial,  $n$  = the number of individuals in each treatment group and  $s$  = the standard deviation of the measurements derived from each treatment group.

An unbiased estimate of the difference in standard deviation units suitable for small sample size (Hedge's  $d$ ) was calculated from Hedge's  $g$  as:

$$\text{Hedge's } d = \text{Hedge's } g (1 - (3 / (4 (n_1 + n_2 - 2) - 1))) \quad (\text{Hedges \& Olkin 1985})$$

The magnitude of Hedge's  $d$  statistics were grouped into small ( $< 0.2$ ), medium (0.21 to 0.79) and large ( $> 0.8$ ) ranges for the purpose of discussion (Cohen 1988).

Overall, 16 studies were included with data from 11 studies for prediction of growth curve, and 11 studies for reproductive development of male sheep offspring.

## Results

### Live weight

Fig. 1 shows the predicted live weight of male offspring from conception to 800 days of age. The live weight of male offspring from either the Control or Restricted dam feeding during pregnancy groups were significantly different ( $P = 0.02$ ). The effect was in the expected direction whereby the Restricted group had a slower growth rate compared to the Control group. There was a significant age effect ( $P < 0.001$ ) for overall live weight.

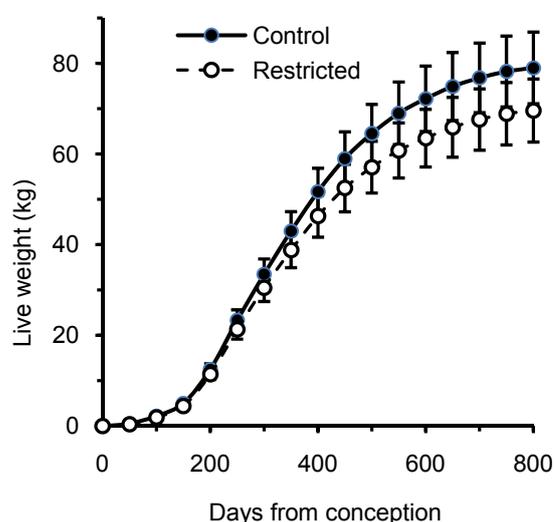
### Reproductive development

Table 3 shows that, there was no significant difference ( $P > 0.05$ ) for testis weight, seminiferous tubule diameter or Sertoli cell count of male sheep offspring between the Control and Restricted dam feeding during pregnancy groups. However, the Control group showed a higher testosterone concentration ( $P = 0.004$ ) than the Restricted group. The mean point estimates of the unbiased difference between trial means in standard deviation units (Hedge's  $d$ ) showed a small effect between the Control and Restricted groups of 0.02 for testis weight, 0.18 for testosterone concentration and 0.14 for seminiferous tubule diameter. The effect was larger (0.38) for Sertoli cell count. There was a significant effect of age for testis weight ( $P < 0.001$ ) and testosterone concentration ( $P < 0.001$ ), with no significant effect of age for seminiferous tubule diameter ( $P = 0.36$ ) or Sertoli cell count ( $P = 0.68$ ).

### Discussion

Maternal nutrition during pregnancy is crucial for fetal growth. It can influence pregnancy success, birth weight and subsequent post-natal growth and reproductive development of offspring (Godfrey & Barker 2000; Redmer et al. 2004). During pregnancy there are a number of developmental processes that impact on fetal development (Rhind 2004). Epidemiological studies indicate that maternal nutrition can influence the pre-natal growth trajectory and the physiology and development of major organ systems (Robinson et al. 1999) with the effects lasting through into later life.

**Figure 1** Predicted live weights (Mean  $\pm$  SE) (using a logistic function) of male offspring from conception to 800 days for Control and Restricted maternal nutrition treatments during pregnancy using eleven sheep studies.



**Table 3** Back-transformed mean  $\pm$  standard error of mean and corresponding Hedges'  $d$  statistic of testis weight (eleven studies), testosterone concentration (three studies), seminiferous tubule diameter (three studies) and Sertoli cell count (three studies) of pre-natal tramping from a minimum of 30 days gestation to a maximum of 301 post-natal days of age born to ewes that were controlled or restrictively fed during pregnancy. m = Number of value means used for meta-analysis where the number of sheep used to obtain each mean ranged from 4 to 14. Bolding of P value indicates significance ( $P < 0.05$ ).

Measurements	Treatment				P value	Hedge's $d$
	m	Control	m	Restricted		
Testis weight (mg)	17	528 $\pm$ 3	39	464 $\pm$ 3	0.18	0.02
Testosterone concentration (ng/mL)	59	1.9 $\pm$ 0.7 <sup>b</sup>	79	1.3 $\pm$ 0.5 <sup>a</sup>	<b>0.004</b>	0.18
Seminiferous tubule diameter ( $\mu$ m)	3	100 $\pm$ 2	4	79 $\pm$ 2	0.26	0.14
Sertoli cell count (per tubule)	3	12.6 $\pm$ 0.1	4	10.0 $\pm$ 1.2	0.38	0.31

<sup>ab</sup>Means between columns within rows with differing superscripts are significantly different ( $P < 0.05$ ).

In this study only sixteen papers were identified for inclusion in the meta-analysis which limits the power of the analysis. Results achieved by using both, the NLMIXED & MIXED procedures estimates of the effects were all in the expected direction where the group of male progeny born following restricted feeding of the dam during pregnancy all had a lower performance than the Control group (Fig. 1 and Table 3).

#### **Live weight**

The results from comparative meta-analysis demonstrated that maternal nutrition restriction during pregnancy altered the growth of male sheep offspring (Fig. 1). This is in agreement with several studies in rats (Léonhardt et al. 2003) and pigs (Kind et al. 2002) which showed that maternal nutrition restriction during pregnancy reduced fetal weight, birth weight or live weight of male offspring. In contrast though, some studies (Zambrano et al. 2005; Long et al. 2010), demonstrated that there was no effect of maternal nutrition restriction on male offspring fetal weight, birth weight, or live weight. However, the meta-analysis of sheep growth to account for differences between studies provides quantitative and qualitative evidence, that nutrition during pre-natal life can alter the live weight performance of male offspring.

Physiologically, growth that results in enlargement of cells in foetal tissue and development that results in changes of the structure and function of cells in foetal tissue are complex biological events that are sensitive to maternal nutrition with a potential carry-over effect in later life (Wu et al. 2006). On average maternal nutrition restriction during gestation is likely to adversely affect male offspring live weight up to about two years of age.

#### **Testis weight**

Our meta-analytic results suggest that maternal undernutrition is unlikely to affect the testis weight of male sheep offspring. This was consistent with several studies (Léonhardt et al. 2003; Sullivan et al. 2010) which showed that maternal nutrition during

pregnancy did not alter testis weight of male offspring. Only two studies by Liang & Zhang (2006) and Genovese et al. (2010) showed testis weight of male offspring was reduced from mothers exposed to restricted nutrition during pregnancy. From a physiological perspective undernutrition during pre-natal life in sheep would not be expected to be critical for fetal testis weight as the development and cell differentiation in the testis is almost complete by Day 100 of pregnancy when the energy requirement for fetal development is low relative high fetal metabolic activity.

#### **Testosterone concentration**

The three studies in this analysis all showed a small ( $d = 0.185$ ) but significant difference of testosterone levels between the Control and Restricted maternal nutrition groups. Other studies have reported variable responses. Zambrano et al. (2005) and Liang & Zhang (2006) reported reduced and Sullivan et al. (2010) reported no effect on testosterone concentration in male offspring following a restriction in maternal nutrition during pregnancy. These inconsistent findings may be due to variation among studies between treatment and control fetuses.

However, the meta-analysis results are consistent with the changes of hypothalamic-pituitary axis secretion due to pre-natal undernutrition (Rhind et al. 2001), thereby reducing plasma testosterone concentration (Zambrano et al. 2005). More testosterone concentration data are required before conclusive statements regarding the effect of maternal nutrition on offspring testosterone levels can be made.

#### **Seminiferous tubule diameter and Sertoli cell count**

The meta-analyses demonstrated that there were no statistically significant differences between the Control and Restricted dam nutrition during pregnancy groups for seminiferous tubule diameter and Sertoli cell count. Data for these two measurements was limited (Table 3) such that it was not possible to draw any sensible conclusions.

As with testosterone concentration, reports on the effect of restrictions to maternal nutrition during pregnancy have been associated with no change (Genovese et al. 2010), or a decrease in seminiferous tubule lumen diameter (Léonhardt et al. 2003) in male offspring. Similarly the restriction to maternal nutrition during pregnancy has been associated with a decrease (Genovese et al. 2010) in Sertoli cell count.

In rams, nutrition not only alters the output of GnRH and testis weight but also the efficiency of spermatogenic tissues such as seminiferous tubule diameter and Sertoli cells count (Martin et al. 2010). Brooks & Thomas (1995) also showed that a reduction of testis weight at birth was positively related to the number of Sertoli cells, while the diameter of seminiferous tubules was highly correlated to the number of Sertoli cells (Hochereau-de Reviers et al. 1987). Therefore, the lack of a difference in testis weight shown in this study is consistent with there being no differences in either the diameter of seminiferous tubules or the Sertoli cell count.

## Conclusions

Our quantitative and qualitative reviews both indicated that maternal nutrition during gestation altered growth and had minor effects on the reproductive development of male offspring. Although there were only a limited number of studies, meta-analysis results showed similar outcomes for growth and reproductive development in male offspring, with those offspring born to dams experiencing restricted nutrition during pregnancy having lower performance compared to the Control group. However, there still appears to be a need for future studies to determine those critical levels of restriction and critical time windows of restriction application that lead to changes in the regulation of cell development. Also, studies are required to investigate further the effect of restricting specific dietary components, such as protein, from the maternal diet during gestation that can affect the pre-natal and subsequent post-natal growth and reproductive development of male offspring. Since profitability in the livestock industry is dependent on the efficiency of animal production characteristics such as growth and reproductive efficiency these additional studies are economically justifiable.

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