The Role of the Small Intestine in Developmental Programming: Impact of Maternal Nutrition on the Dam and Offspring[1,2]

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Introduction

Small intestinal growth and function are critical for optimal animal growth and health, playing a major role in nutrient digestion and absorption, energy and nutrient expenditure, and immunological competence. Small intestinal growth and development are often overlooked but essential processes driving metabolism, immunology, survival, and growth. The small intestine not only serves as the main site for digestion and absorption of nutrients, but it is also a major energy and nutrient sink due to its high metabolic activity and rapid turnover. Changes in small intestinal mass, cellularity, and oxygen consumption have been demonstrated during feed restriction and in response to specific nutrients. The effects of in utero environment have become a major area of study in animal and human nutrition, physiology, and epidemiology research, as evidenced by the hundreds of reviews on the subject. In livestock, intrauterine growth restriction (**IUGR**) results in impaired fetal development, low birth weight offspring, and decreased long-term production. Programming of growth and development in livestock may be driven by many factors, but often occurs in response to compromised nutrient supply to developing offspring. Because the small intestine is critical to animal growth, health, and production and is responsive to its luminal and extraluminal environment, early life effects on small intestinal development likely play a significant role in observed programming of later animal health and performance, including the acquisition of nutrients during the pre- and postnatal periods. Additionally, impacts of gestational nutrition on the maternal small intestine may change nutrient delivery to offspring, both in utero and during lactation. This review will focus on impacts of nutrition during pregnancy on maternal and offspring small intestines and focus on data from ruminant livestock models.

Fetal Small Intestinal Growth and Development

There are multiple developmental windows (**Figure 1**) for the small intestine

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during fetal, perinatal, and neonatal periods. Organogenesis generally occurs during early to mid-gestation, followed by rapid fetal growth in the last third of gestation, then preparation for the transition from the uterine to the outside environment during the perinatal period. In addition to these windows, the small intestine continues to develop postnatally and even into maturity, when it remains plastic and responds to physiological state, diet, and other factors.

Evidence of Developmental Programming of the Offspring Small Intestine Intrauterine Growth Restriction

Effects of IUGR on the small intestine (**Table 1**) generally include reduced mass and/or length of the small intestine, decreased villus and crypt density, villus height and/or width, crypt depth, and mucosal size which suggest that reduced mass may also be accompanied by reduced functional area and development. Additional decreases in proliferation and cellular differentiation suggest altered crypt proliferative dynamics. Although effects of IUGR on the small intestine have been better characterized prenatally or immediately after birth, these effects persist postnatally.

Gene expression in the small intestine has also been altered by IUGR. Piglets identified as IUGR had altered jejunal protein expression, including 7 down-regulated and 4 up-regulated genes. Altered ileal gene expression was also observed in IUGR compared with normal piglets, although these were affected by day of sampling (birth vs. d 2 or 5 postnatally). At each time point, genes differentially expressed included those involved in macromolecule metabolism, biosynthesis, and cellular metabolism.

Although many of the reported effects of IUGR on the small intestine appear to be negative, this is not always the case. For example, jejunal lactase and maltase were greater for IUGR rats than control rats at birth, although this did not extend past the immediate postnatal period (Qui et al., 2005). These authors suggested that increased digestive enzyme production at birth was an adaptive mechanism allowing IUGR neonates to have increased digestive capacity. In another study, ileal adherent bacterial numbers were increased for IUGR pigs at d 2 postnatally (D'Inca et al., 2010), indicating that IUGR can alter bacterial colonization of the small intestine postnatally.

Maternal Nutrient Manipulation during Gestation

Research indicates that both maternal nutritional plane (**Table 2**) and specific nutrient intake can affect the fetal small intestine. Timing of these maternal nutritional insults is important due to the developmental windows outlined in **Figure 1**.

Fetal. Nutrient restriction during early and mid-gestation does not appear to impact fetal small intestinal growth. Nutrient restriction during early and mid-gestation can increase jejunal crypt proliferation at d 125 of gestation in fetal calves. Additionally, when nutrient-restricted cows were realimented, total vascularity of the fetal small intestine was increased at d 245 of gestation. These data suggest that nutrient restriction increased the efficiency of the fetal small intestine, perhaps similarly to the

“thrifty phenotype” hypothesis (Hales and Barker, 1992), which has been postulated to describe fetal development changes that increase survival in the face of a negative environment or poor nutrition (Wells, 2007).

Maternal nutrient restriction of ewes in mid- and late gestation has decreased small intestinal mass and jejunal hypertrophy (protein:DNA), despite a lack of differences in jejunal proliferation. Lambs from nutrient- restricted ewes had decreased total jejunal microvascular volume concurrently with reduced jejunal mRNA expression of soluble guanylate cyclase (**GUCY1B3**), a NO receptor involved in vasodilation and angiogenesis. Conversely, small intestinal mass of fetal lambs from ewes that were nutrient restricted during the last 3 wk of gestation was unaffected, suggesting that longer periods of maternal nutrient restriction are necessary to affect the fetal small intestine. Nutrient restriction during mid- and late gestation has increased oxygen consumption per unit of small intestine in late-term fetal lambs.

Postnatal. Changes in maternal nutrition in late gestation may negatively affect gut maturation. Cortisol and fetal swallowing of amniotic fluid both play an important role in the small intestinal maturation process (Sangild et al., 2000; Trahair and Sangild, 2004). For example, expression of vascular endothelial growth factor (**VEGF**) in the fetal small intestine, which is important for angiogenesis of the growing tissue, is likely cortisol-dependent in sheep (Holmes et al., 2008). Maternal cortisol levels are often changed by gestational plane of nutrition (Symonds et al., 2007; Lemley et al., 2014), and nutrient content of the amnion has been altered by nutrient restriction in ewes (Kwon et al., 2004), indicating that maternal nutrition may have an even greater impact during final prenatal maturation. Small intestinal function is particularly important in livestock species that rely upon transfer of passive immunity from immunoglobulins in colostrum (e.g. cattle and sheep). Colostrum also contains a cadre of growth factors, hormones, and nutrients which are crucial for small intestinal development (Quigley et al., 1988; Xu, 1996; Sangild et al., 2000; Berni Canani et al., 2008). Colostrum production has been decreased by both nutrient restriction and over nutrition in ewes (Swanson et al., 2008; Meyer et al., 2011), which could also have further implications in perinatal small intestinal maturation.

There are few data from ruminant developmental programming models investigating small intestinal parameters postnatally. Two studies have investigated postnatal lamb small intestinal growth and vascularity after mid- and late gestation nutrient restriction or over-nourishment (**Table 2**). These data demonstrate that 20-d old lambs have continued alterations in jejunal hyperplasia, vascularity, and gene expression, even when lambs were fed a common artificial colostrum and milk replacer after birth and managed together. Moreover, jejunal proliferation, vascularity, and gene expression were also affected by gestational nutrition in 180-d old lambs in a similar model, demonstrating that changes to the small intestine may persist well into life. In both 20- and 180-d old lambs, glucagon-like peptide 2 (**GLP-2**) expression was altered, although in opposite ways (**Table 2**). This GLP-2 is very important for small intestinal development, including growth and vascularization, making it a possible mechanism for small intestinal changes observed in these studies.

It has also been demonstrated that maternal intake of specific nutrients such as selenium during gestation can impact fetal small intestinal development. Fetuses from ewes fed supranutritional selenium throughout gestation had increased jejunal hypertrophy and decreased jejunal VEGF mRNA expression. In addition, form and level of maternal selenium supplementation during gestation have impacted fetal jejunal hypertrophy. Even when lambs were fed similar diets postnatally, high selenium during gestation has continued to impact lamb jejunal measures at d 20 and 180 of age, suggesting long-term impacts of this micronutrient fed prenatally or compensation by offspring after normal selenium intakes postnatally.

Maternal Small Intestinal Adaptations

Adaptation to Nutrient Manipulation

Nutritional Plane. Small intestinal growth and function are known to change with nutrient intake, so it should come as no surprise that they change with nutritional plane during pregnancy. Most of the studies cited here include treatments that vary in nutrient intake and bulk density of feed, both of which impact the small intestine. These studies investigating impacts of nutritional plane during gestation on ruminant small intestinal mass, proliferation, vascularity, and gene expression are summarized in **Table 3**.

In general, alteration of nutritional plane during early gestation alone does not seem to affect mass of the ruminant small intestine (**Table 3**), even though over nutrition during this period increased indices of jejunal hypertrophy. Impacts of nutrient restriction during early and mid- or mid-gestation are more variable. These have either decreased or not affected maternal small intestinal mass when measured immediately after nutrient restriction. Dams rebounded when nutrient restriction was followed by realimentation in late gestation, and small intestinal mass was not different from controls near term.

In most studies, small intestinal mass has responded to nutritional plane during both mid- and late gestation or late gestation only when measured at the end of the restriction period (**Table 3**). Changes in cellularity have been observed in these studies indicating that both hypertrophy and hyperplasia may play a role in growth differences, even when no change in mass was observed. Despite differences in mass and cellularity, no differences have been observed in jejunal crypt cell proliferation due to nutritional plane. This is likely because tissues were collected from ewes after long periods (40 to 80 d) of nutrient restriction in these studies. Alterations in proliferative rate necessary to change small intestinal mass may have occurred much earlier during nutrient restriction, and the tissues most likely reached steady-state by late gestation. Small intestinal adaptation has been detected as soon as 5 to 14 d after dietary changes, supporting this hypothesis. Little is known about the impacts of gestational nutrition on small intestinal energy use, but one study reported that oxygen consumption was increased per unit of tissue in nutrient-restricted ewes. Jejunal vascularity has responded to nutritional plane during gestation in several studies in ewes (**Table 3**).

The mechanisms of adaptation to altered nutritional plane during gestation in both growth and vascularity of the ruminant small intestine are not well known, but angiogenic and vasoactive factor gene expression may play a role. Expression of VEGF and NO systems have been altered in ewes (**Table 3**), although some of these data are contradictory. Jejunal mRNA expression of VEGF and its receptors, FLT1 and KDR, were greater for nutrient-restricted ewes in late gestation, suggesting that up-regulation of angiogenic factors was occurring in the face of reduced small intestinal growth and vascularization. Jejunal expression of VEGF and endothelial NO synthase 3 (**NOS3**) have also been increased after over nutrition during pregnancy (Meyer et al, 2013). In vitro systems have demonstrated that VEGF delivery to the small intestine increases vascularity (Rocha et al., 2008), suggesting that the small intestine of both nutrient restricted and over-nourished ewes may use VEGF or its receptors to modulate vascularization during nutritional insults. It is important to point out that it is uncertain if angiogenic factors influenced vascularization changes earlier in the nutrient-restriction period, as gene expression was only determined at one time point.

Specific Nutrients. There have been few published studies to date investigating the effect of specific nutrient intake during gestation on the maternal small intestine. In a series of studies to determine impacts of supranutritional selenium in ewes during gestation, results have been variable. High selenium diets fed during gestation have had no effect (Neville et al., 2008; Carlson et al., 2009), increased (Reed et al., 2007), and decreased (Meyer et al., 2012) primiparous ewe small intestinal mass. When small intestinal mass was increased, no effects of selenium on cellularity measures, proliferation, or vascularity were observed (Reed et al., 2007). Alternatively, supranutritional selenium decreased DNA concentration in other studies (Neville et al., 2008; Carlson et al., 2009), with proliferative rate of crypt cells unaffected (Carlson et al., 2009) or increased by selenium (Neville et al., 2008). Expression of the VEGF and NO systems has been impacted by high selenium, where supranutritional selenium has reduced mRNA of VEGF and its receptors (Neville et al., 2010; Meyer et al., 2012). Selenium has been hypothesized to decrease cancerous tumor growth and vascularization (Zeng and Combes, 2008), thus actions of selenium on proliferation and vascularity of the small intestine may have similar mechanisms. When high selenium was removed from the diet during lactation, small intestinal mass of ewes increased within the first 20 d to that of control-fed ewes (Meyer et al., 2012). It is unclear what caused differences in responses to high selenium in these studies, although selenium source and level of supplementation appear to alter small intestinal response (Neville et al., 2008; 2010), and thus likely influenced results.

Future Directions

The small intestine is a dynamic, rapidly changing tissue that is crucial for animal growth and health. Further research is necessary to better understand the role of the maternal small intestine in providing nutrients to the fetus and postnatal offspring and to advance knowledge of the effects of maternal nutrition on programming of offspring small intestinal growth and function. Additionally, research in the role of epigenetics and the microbiome in programming of the small intestine is in its infancy and can provide a

wealth of knowledge. A better understanding of the effects of gestational nutrition on the maternal and offspring small intestine will allow for development of management and therapeutic strategies to optimize the efficiency of livestock production.

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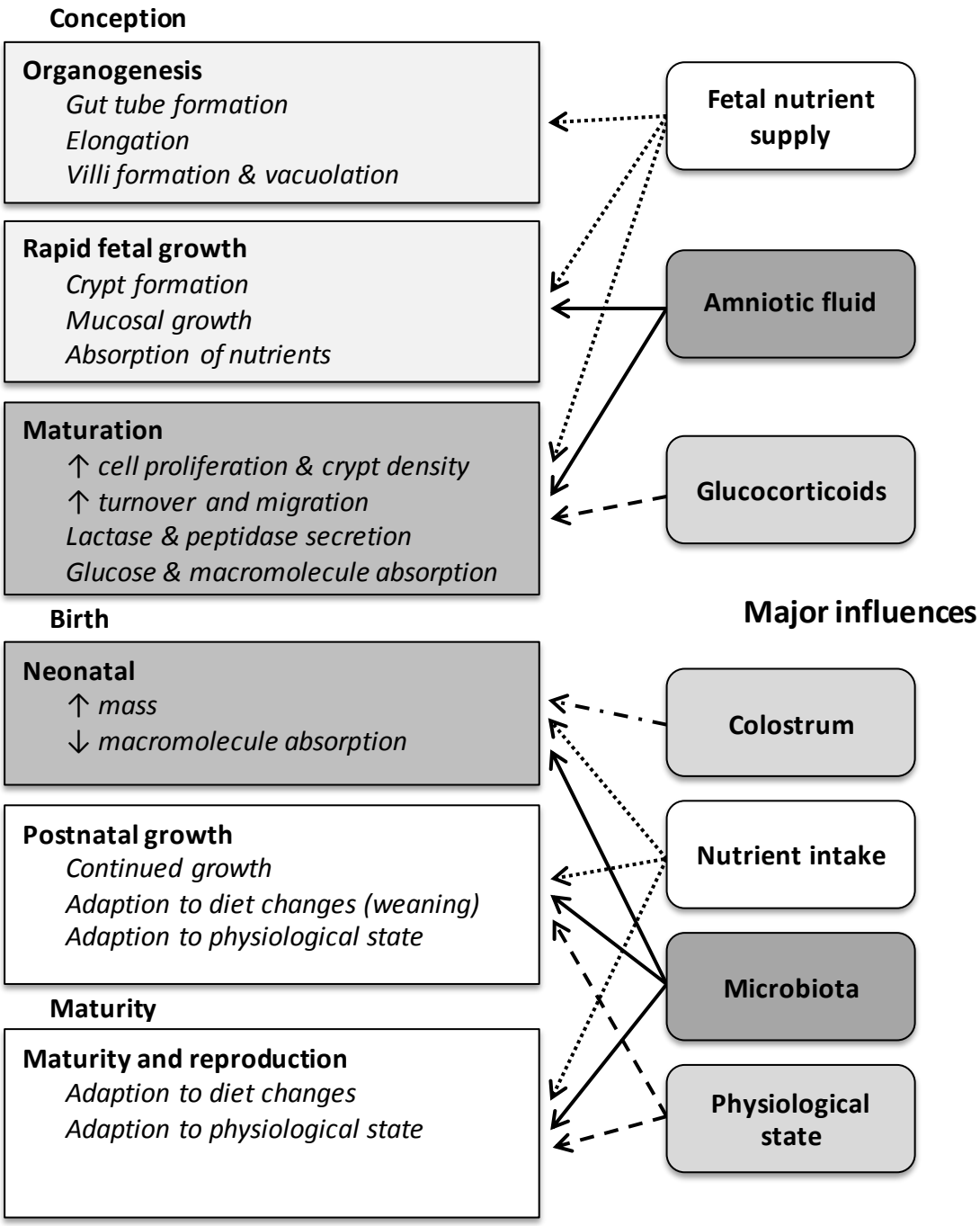

Figure 1. Windows of small intestinal growth and development and their influences. The timing of these events vary with species, but in general organogenesis occurs during early to mid-gestation, rapid fetal growth occurs in mid- to late gestation, and maturation occurs during late gestation, immediately before birth. Adapted from Adv. Nut. 2016. 7:169–178.

Table 1. Impacts of intrauterine growth restriction on the small intestine (Adapted from Adv, Nutr. 2016. 7:169–178).[1]

Reference	Species	Age measured[2]	Small intestinal mass or length response	Additional small intestinal responses
Avila et al., 1989	Sheep	d 140 gestation	↓ mass ↓ length	↓ villus and crypt density ↓ villus height and crypt depth ↓ mucosal thickness
Trahair et al., 1997	Sheep	d 90 gestation	↓ mass ↓ relative mass	↓ mucosal circumference and area ↓ crypt depth ↓ or abnormal enterocyte differentiation
Cellini et al., 2004	Rabbits	d 31 gestation	Not determined	↓ villus height ↓ proliferation ↑ epidermal growth factor mRNA
Qiu et al., 2005	Rats	birth to 12 wk	↓ mass (to 4 wk) ↓ length (to 12 wk)	↑ maltase (at birth) ↑ lactase (at birth)
Wang et al., 2005	Pigs	birth	↓ mass ↓ length	↓ mucosal weight ↓ IGF-1 mRNA expression
Wang et al., 2008	Pigs	birth	↓ mass ↓ relative mass	altered proteome
D'Inca et al., 2010	Pigs	birth to 5 d	↓ mass (to 2 d) ↓ length (to 5 d)	↓ villus height (to 2 d) ↓ villus width (at 2 d) ↑ adherent bacterial number altered transcriptome

[1] IGF-1, insulin-like growth factor 1.
[2] Approximate gestation lengths: sheep = 150 d, rabbit = 31 d.

Table 2. Impacts of maternal nutrition on the ruminant offspring small intestine from selected studies (Adapted from Adv. Nutr. 2016. 7:169–178)[1].

Reference	Species	Treatments	Age measured[2]	Small intestinal mass response	Additional small intestinal responses
Meyer et al., 2010	Cattle	CON vs RES (d 30 to 125 of gestation)	d 125 gestation	NS	↑ proliferation in RES
Meyer et al., 2010	Cattle	CON vs RES (d 30 to 125) and realimented (d 125 to 245)	d 245 gestation	NS	↑ total vascularity in RES and realimented
Meyer et al., 2014	Cattle	CON vs RES vs RES + AA supplement (d 45 to 185 gestation)	~450 d postnatal	NS	↑ GUCY1B3 mRNA in RES + AA
Prezotto et al., 2014	Sheep	CON vs RES (d 50 to 130 of gestation)	d 130 gestation	NS	↓ protein concentration in RES ↑ oxygen consumption in RES
Reed et al., 2007; Neville et al., 2010	Sheep	CON vs RES (d 64 to 135 of gestation)	d 135 gestation	↓ in RES	↓ total vascularity in RES ↓ protein:DNA in RES ↓ GUCY1B3 mRNA in RES

Meyer et al., 2010; 2013	Sheep	CON vs RES (d 40 of gestation to birth)	d 20 postnatal	NS	↓ total vascularity in RES ↓ capillary surface density in RES ↑ capillary size in RES ↑ GLP-2 mRNA in RES ↓ postnatal weight gain in RES
Yunusova et al. (55)	Sheep	CON vs RES (d 50 gestation to birth)	d 180 postnatal	NS	↓ capillary size in RES ↓ total proliferation in RES ↓ GLP-2 mRNA in RES
Meyer et al. (85, 86)	Sheep	CON vs OVR (d 40 of gestation to birth)	d 20 postnatal	NS	↑ DNA concentration in OVR
Yunusova et al., 2013	Sheep	CON vs OVR (d 50 of gestation to birth)	d 180 postnatal	NS	↓ total proliferating cells in OVR

[1] CON: control nutritional plane (near nutrient requirements); GLP-2: glucagon-like peptide 2; GUCY1B3: soluble guanylate cyclase (NO receptor); NS: not significant ($P > 0.10$); OVR: over nutrition; RES: nutrient restriction; RES + AA: nutrient restriction with protein supplementation to meet essential AA of control.
[2] Approximate gestation lengths: cattle = 285 d, sheep = 150 d.

Table 3. Impacts of gestational nutrition on maternal small intestine from selected studies (Adv. Nutr. 2016. 7:169–178)[1].

Reference	Species, parity	Treatments	Stage measured[2]	Small intestinal mass response	Additional small intestinal responses
Meyer et al., 2010	Cattle, Multiparous	CON vs RES (d 30 to 125 gestation)	d 125 gestation	NS	↓ RNA:DNA in RES
Meyer et al., 2010	Cattle, Multiparous	CON vs RES (d 30 to 125) and realimented (d 125 to 245)	d 245 gestation	NS	↓ RNA:DNA in RES
Scheaffer et al., 2004a,b	Sheep, Multiparous	CON vs RES (d 50 to 90)	d 90 gestation	↓ in RES	↓ DNA concentration in RES ↑ capillary area density in RES
Carlson et al., 2009	Sheep, First	CON vs RES (d 50 to 90)	d 130 gestation	NS	NS
Carlson et al., 2009	Sheep, First	CON vs RES (d 50 to 130)	d 130 gestation	↓ in RES	↓ DNA concentration in RES
Scheaffer et al., 2004a,b	Sheep, Multiparous	CON vs RES (d 50 to 130)	d 130 gestation	↓ in RES	↑ DNA concentration in RES ↑ capillary area density in RES
Prezotto et al., 2014	Sheep, First	CON vs RES (d 50 to 130)	d 130 gestation	↓ in RES	↑ oxygen consumption in RES
Carlson et al., 2009	Sheep, First	CON vs RES (d 90 to 130)	d 130 gestation	↓ in RES	↑ RNA concentration in RES

Reed et al., 2007; Neville et al., 2010	Sheep, First	CON vs RES (d 64 to 135)	d 135 gestation	↓ in RES	↓ total vascularity in RES ↓ capillary area density in RES ↓ capillary size in RES ↑ VEGF, FLT1, KDR mRNA in RES ↑ NRP1, NRP2 mRNA in RES
Meyer et al., 2012	Sheep, First	CON vs RES (d 40 to parturition)	d 0 post-partum	NS	↓ RNA concentration and RNA:DNA in RES ↓ capillary surface density in RES ↓ mucosal density in RES
Meyer et al., 2012	Sheep, First	CON vs RES (d 40 to parturition)	d 20 post-partum	NS	↑ proliferation in RES ↓ capillary surface density in RES
Caton et al., 2009	Sheep, First	CON vs OVR (d 0 to 50)	d 50 gestation	NS	↑ RNA concentration and RNA:DNA in OVR
Caton et al., 2009	Sheep, First	CON vs OVR (d 0 to 90)	d 90 gestation	↑ in OVR	↑ RNA concentration and RNA:DNA in OVR
Caton et al., 2009	Sheep, First	CON vs OVR (d 0 to 130)	d 130 gestation	↓ in OVR	↑ RNA concentration in OVR
Meyer et al., 2012	Sheep, First	CON vs OVR (d 40 to parturition)	d 0 post-partum	↑ in OVR	↓ RNA concentration and RNA:DNA in OVR ↑ total vascularity in OVR ↑ VEGF, FLT1 mRNA in OVR ↑ NOS3 mRNA in OVR
Meyer et al., 2012	Sheep, First	CON vs OVR (40d to parturition)	d 20 post-partum	NS	↓ proliferation in OVR ↑ total vascularity in OVR

[1] CON: control nutritional plane; FLT1: VEGF receptor 1; KDR: VEGF receptor 2; NOS3: endothelial nitric oxide synthase 3; NRP1: neuropilin 1; NRP2: neuropilin 2; NS: not significant ($P > 0.05$); OVR: over nutrition; RES: nutrient restriction; VEGF: vascular endothelial growth factor.

[2] Approximate gestation lengths: cattle = 285 d, sheep = 150 d.

SESSION NOTES