Journal of Developmental Origins of Health and Disease

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Livestock models of maternal nutrition and developmental programming

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Review

Cite this article: Swanson RM, Davila Ruiz BJ, Hurlbert JL, Diniz WJS, Banerjee P, Dahlen C, Crouse MS, Hauxwell KM, Caton JS, and Reynolds L. (2026) Livestock models of maternal nutrition and developmental programming. *Journal of Developmental Origins of Health and Disease* **17**: e14, 1–22.
doi: 10.1017/S2040174426100452

Received: 17 January 2025
Revised: 22 December 2025
Accepted: 15 January 2026

Keywords:
Developmental programming; livestock models; maternal nutrition; postnatal health and productivity

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Abstract

Developmental programming has emerged as one of the major biological principles and biomedical issues of this century because of its potential for long-term, even transgenerational, effects on the health and productivity of offspring. Livestock models have been widely used to establish the mechanisms of developmental programming in fetuses and offspring, and accordingly present data with dual benefits; both serving animal agricultural purposes and providing insights for biomedical applications. Livestock models have furthered our understanding of how developmental processes can influence postnatal health and productivity in the short- and long-term. In addition, because livestock are key to agricultural sustainability and food security, studies in livestock contribute to human livelihood. In this review, we will focus on the influence of maternal nutrition in livestock models on developmental outcomes. Maternal nutritional models include global nutrient intake (over- and under-nutrition) and supplementation of specific macro and micronutrients. Specifically, we will review the effects of maternal nutrition on: placental function, key metabolic tissues of the fetus/offspring (visceral tissues, skeletal muscle, and immune system), genetics, epigenetics, and transgenerational programming, parturition, and the underlying mechanism of developmental programming. Lastly, we will focus on gaps in knowledge and future research directions.

Introduction

Developmental programming is the concept that factors affecting development, primarily during the fetal and neonatal periods (although gametes can also be affected), do so by altering gene expression and therefore development and function of various organ systems in the short- and long-term.[1–5] In addition, such effects on organ development and function can affect the health and well-being of the offspring during adulthood and even among subsequent generations.[6,7] Based on initial epidemiological studies in humans, parental nutrition was hypothesized to have a major influence on developmental programming, and subsequent epidemiological studies in humans as well as controlled studies in various animal models have confirmed this hypothesis[4,5,8–11] (see summary **Table 1 where we have highlighted the repeatability of findings and effects within each topic covered herein**).

Much of the focus in developmental programming research has been on its negative effects on health, productivity, and even longevity of the offspring. However, it has been argued that developmental programming has remained in the genome because it is ultimately adaptive.[9,12,13] In the long run, the effects of developmental programming must be positive overall. This is an important concept if we are to understand and perhaps even develop strategies to manage developmental programming for potential benefits to animal agriculture, as well as human health and wellbeing.

Our focus in this manuscript is to: 1) briefly review maternal nutrition-driven, and to some extent paternal nutrition-driven, livestock models of developmental programming with an understanding that these models are dual purpose with dual benefit for both livestock productivity and human health, 2) address placental development and its potential effects on nutrient supply to the conceptus, 3) describe the programming of the genetic and epigenetic landscape, 4) discuss programming of key tissues, including viscera and skeletal muscle, and the immune system, 5) discuss the programming of parturition, and 6) suggest future research directions and needs.

Livestock models of developmental programming: dual purpose with dual benefit for both livestock and humans

Livestock models have and will continue to contribute significantly to our understanding of the fundamental biological mechanisms associated with growth, development, and well-being.

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https://doi.org/10.1017/S2040174426100452 Published online by Cambridge University Press

Table 1. Some livestock models of maternal nutrition and developmental programming

Treatment	Day of gestation	Species and parity	Responses	Reference	Year	doi
Overnutrition (HI) vs Control (CON)	Day 4 (embryo transfer) to parturition	Sheep, adolescent nulliparous	• Birth: ↑ incidence of very preterm & preterm delivery (>50%), extremely low & low birthweight (>50%) in HI ewes • Birth: ↓ placenta, COT, & lamb weights from HI ewes • Birth: ↓ colostrum yield & ↑ feeding assistance needed in lambs from HI ewes	Wallace et al., PLOS ONE., 16(11)	2021	10.1371/journal.pone.0259890
High intake (HI) vs moderate intake (CON)	Day 4 (embryo transfer) to 81	Sheep, nulliparous	• Day 81: no differences in placentome weight or number, or fetal body, brain, or liver weights • Day 81: ↓ VEGF, ANGPT1, ANGPT2, NOS3 & FLT1 transcript abundance in HI ewes • Day 81: VEGF & maternal weight gain and VEGF & fetal weight were negatively correlated • Day 81: ↓ placenta cell proliferation in HI ewes	Redmer et al., Biol. of Reprod., 72(4):1004-1009	2005	10.1095/biolreprod.104.037234
Underfed (UN) vs Overfed (HI) vs Control (CON) with Adequate (Ase) or High (Hse) selenium	Se: Day 0 (breeding) to parturition Diet: Day 40 or 50 to parturition	Sheep, nulliparous or primiparous	• Parturition: ↓ gestation length & COT weights in HI ewes • Parturition: ↓ colostrum weight & volume, and total IgG production in HI & UN ewes • Birth: ↓ cortisol in offspring from Hse ewes and RES ewes & T_3 in offspring from RES ewes & T_4 in offspring from HI ewes • Postnatal day 20: ↑ large intestine mass in lambs from CON-Hse & HI-HSe vs RES-Hse • Postnatal day 20: ↑ pancreas weight in lambs from RES-HSe, CON-HSe & HI-ASe vs all other groups • Postnatal day 20: ↑ small intestine cell proliferation in lambs from HI-ASe vs all other groups • Postnatal day 20: ↓ jejunal capillary surface density in lambs from RES vs CON & HI • Postnatal day 57: ↓ morbidity in lambs from RES-HSe ewes compared with all other groups • Postnatal days 107 & 148: ↑ glucose stimulated insulin secretion in RES-HSe compared with RES-Ase and CON-HSe	Camacho et al., Reproduction., 144(1):23-35 Swanson et al., J. Anim. Sci. 86:2415-2423 Meyer et al., J. Anim. Sci. 91:6:2628-2639 Hammer et al., J. Anim. Sci. 89:11:3690-3698 Vonnahme et al., et al., Dom. Anim. Endocrin. 39:4:240-248	2012 2008 2013 2011 2010	10.1530/REP-11-0302 10.2527/jas.2008-0996 10.2527/jas.2012-5953 10.2527/jas.2010-3724 10.1016/j.domaniend.2010.06.005
Underfed (UN) vs Control fed (CON)	Day 4 (embryo transfer) to 89 or 130	Sheep, primiparous	• Day 89: ↓ perirenal fat mass & mRNA for IGF1, IGF2, IGF2R, PPARγ, LPL and leptin • Day 130: ↓ Fetal weight & circulating glucose and insulin	Wallace et al., J Molec Endocrinol 54:263-75	2015	10.1530/JME-15-0048
Overfed (HI) vs Control fed (CON)	Day 4 (embryo transfer) to 130	Sheep, primiparous	• ↓ fetal and placental weights; maternal circulating GH; fetal circulating O2, glucose, insulin & IGF-1; gestation length – day 142 in HI vs. day 145 in CON • ↑ fetal brain:liver weight, perirenal fat mass, circulating lactate; maternal circulating insulin & IGF-1	Wallace et al., Placenta 27 (Supplement A) Trophoblast Research 20:S61-S68.	2006	10.1016/j.placenta.2005.12.002
Nutrient restricted (RES) vs Overfed (OVER) vs Control (CON)	Day 116 to parturition	Sheep, primiparous & multiparous	• Postnatal: ↓ birth weight & heart girth, and backfat at 3 mos in lambs from RES ewes vs OVER & CON • Postnatal: ↓ IFG1 at birth & 3 mos in lambs from RES ewes vs OVER & CON • Postnatal: ↓ IFGBP3 at birth & 3 mos in lambs from RES & OVER ewes vs CON • Postnatal: ↑ leptin at birth & 3 mos in lambs from OVER ewes vs RES & CON	Hoffman et al., Dom. Anim. Endocrin., 49:39-48	2014	10.1016/j.domaniend.2014.05.002

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Table 1. (*Continued*)

Underfed (UN) vs Control fed (*ad libitum*; CON)	60 days before mating to day 30 after mating, then fed as CON (*ad libitum*)	Sheep, multiparous	• Day −60 to +30: ↓ maternal circulating cortisol & ACTH • Day 37-93: ↓ maternal circulating P4 • Day 107-delivery: ↓ maternal circulating oPL	Bloomfield et al., Science 300:606	2003	10.1126/science.1080803
			• Day 127-131: Early maturation of the fetal HPAA (↑ response to metyrapone block of P450c11$\beta 1$) • day 120-140: ↑ fetal circulating cortisol by half of the UN fetuses & ↑ ACTH in all UN fetuses	Bloomfield et al., Endocrinology 145:4278-85	2004	10.1210/en.2004-0424
			• Parturition: ↓ gestation length – day 133-139 in UN vs. day 145-146 in CON • Postpartum: "... all preterm lambs died soon after birth."	Kumarasmay et al., Am J Physiol 288:R67-R72	2005	10.1152/ajpregu.00357.2004
Underfed (SGA and NonSGA; UN) vs Control fed (CON)	Day 35 to 135, all sheep were impregnated by embryo transfer (day 6)	Sheep, multiparous	• Day 135: ↓ maternal body, gastrocnemius muscle & liver weights in UN ewes • Day 135: ↓ placentome weights in NR SGA vs NR NonSGA and CON	Steinhauser et al., Biol. Reprod. 101:1:170-180	2020	10.1093/biolre/ioaa180
			• Day 35 to 135: ↓ maternal T_4 in NR SGA vs NR NonSGA and CON & ↑ T_3 in NR NonSGA vs NR SGA and CON • Day 135: ↓ T_4 in UN fetuses vs CON	Steinhauser et al., Domest. Anim. Endocrinol. 77	2021	10.3390/ijms22147654
			• Day 70 & 135: differential gene expression & pathway enrichment in placentomes across groups (cytokine activity, receptor binding, protein binding, etc.)	Steinhauser et al., Int. J. Mol. Sci. 22:7654	2021	10.1016/j.domaniend.2021.106632
			• Day 135: ↓ fetal body weight, crown rump length, sternum & heart circumference, several organs in NR SGA vs NR NonSGA & CON • Day 135: ↓ fetal skeletal muscle weights, myofiber number, myonuclei per myofiber in NR SGA vs NR NonSGA & CON	Sandoval et al., Domest. Anim. Endocrinol. 72	2020	10.1016/j.domanimend.2020.106443
			• Day 135: ↓ fetal circulating insulin and IGF-1 & ↑ skeletal muscle IGF1R in NR SGA vs NR NonSGA & CON	Sandoval et al., Domest. Anim. Endocrinol. 74	2020	10.1016/j.domaniend.2020.106556
Overfed (HI) vs Control (CON) with adequate (Ase) or high (Hse) selenium	Se: Day 0 (breeding) to parturition Diet: Day 40 to parturition	Sheep, multiparous	• Birth: ↑ cytokines transcript abundance & phospho-JNK/JNK protein in neonatal ileum from HI-HSe ewes vs ASe	Wang et al., J. Anim. Sci. 90:325-333	2012	10.2527/JAS.2011-4155
Fiber (HY) vs Starch (CN) vs Fiber, Protein, Fat (DG)	Day 67 to 130	Sheep, multiparous	• Day 130: ↓ gene expression & ribosome, chromatin, and energetic metabolism biological processes in fetal skeletal muscle from CN ewes vs HY & DG • Day 130: ↑ gene expression & dephosphorylation, phosphatase activity, and phosphoric ester hydrolase activity biologic processes in fetal subcutaneous adipose from DG ewes vs HY & CN	Peñagaricano et al., BMC Genomics	2014	10.1186/1471-2164-15-1034
			• Day 130: ↑ gene expression & fetal development biologic processes in fetal perirenal adipose tissue from DG ewes vs CN • Day 130: ↑ DNMTs in fetal subcutaneous and perirenal fat & skeletal muscle from DG ewes	Lan et al., Front. Genet. 4:49	2013	10.3389/fgene.2013.00049
Methyl-deficient diet (MD) vs Control (CON)	8 weeks prior to conception to day 6 of gestation	Sheep, multiparous	• Postnatal: ↑ ADG from birth to weaning, mature body weight in offspring from MD ewes	Sinclair et al., Proc. Natl. Acad.	2007	10.1073/pnas.0707258104

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Table 1. (*Continued*)

Treatment	Day of gestation	Species and parity	Responses	Reference	Year	doi
			• Postnatal: ↑ adiposity, insulin resistance, & blood pressure and ↓ proportion of skeletal muscle in mature male offspring from MD ewes • Day 90: altered fetal liver DNA methylation	Sci., 104(49):19351-19356		
60% metabolizable protein (MP60) vs 80% metabolizable protein (MP80) vs 100% metabolizable protein (MP100)	Day 100 to 130	Sheep, multiparous	• Day 130: ↑ ewe body weight in MP80 vs MP60 • Day 130: ↑ circulating T4 in MP80 ewes vs MP60 vs MP100 • Day 130: ↑ BUN & ↓ calcium in MP100 vs MP80 vs MP60 ewes • Day 130: ↓ fetal body weight per unit of eviscerated body weight in MP60 vs MP80 vs MP100 singleton pregnancies • Day 130: ↑ fetal body weight per unit of eviscerated body weight in MP60 vs MP80 vs MP100 twin pregnancies	Swanson et al., Domest. Anim. Endocrinol., 58:113-125	2017	10.1016/j.domaniend.2015.08.002
Nutrient restricted (RES) vs Nutrient restricted plus arginine (RES+ARG) vs Control (CON)	Day 54 to parturition	Sheep, multiparous	• Postnatal: ↓ lamb birth & 33-day old body weights in RES vs CON but RES+ARG was intermediate (partial rescue) • Postnatal: lamb body weights were similar among all treatments from day 40 to 54 of age (compensatory gain)	Peine et al., J. Anim. Sci., 96:3471-3481	2018	10.1093/jas/sky221
Nutrient restricted (RES) vs Overfed (OVER) vs Control (CON)	Day 30 to parturition	Sheep, multiparous	• Day 90: ↑ Longissimus dorsi muscle primary fibers & ↓ secondary:primary ratio in fetuses from RES & OVER vs CON • Day 90: ↑ semitendinosus muscle primary, secondary & total fibers in fetuses from RES & OVER ewes vs CON • Day 45 & 135: ↓ Pax7+ cells in fetal semitendinosus from RES vs OVER & CON • Day 90: ↓ Pax7+ cells in fetal semitendinosus & triceps brachii from RES & OVER vs CON • Fetal: DEG analysis showed downregulation in skeletal muscle from RES & OVER vs CON	Gauvin et al., J. Anim. Sci., 98:1	2020	10.1093/jas/skz388
			• Day 135: Altered immune gene expression in fetal whole blood & liver from RES & OVER vs CON • Postnatal: No differences in bone mineral content, area, density, or length in offspring femurs & tibias at birth or 3 mos of age	Jones et al., Biol. Reprod., 98(2):184-196	2018	10.1093/biolre/iox174
			• Birth: ↓ basal respiration, maximal respiration & ATP production in lamb bone mitochondria from RES & OVER vs CON • Birth: ↓ mesenchymal stem cell proliferation in lamb bone from RES & OVER ewes	Pillai et al., PLOS ONE., 11(12)	2016	10.1371/journal.pone.0168382
Low gain (LG) vs High gain (HG) with vitamin (VTM) or without (NoVTM)	Day 0 (breeding) to 83	Beef cattle, nulliparous	• Day 83: ↑ ABC and SLC transporter genes in fetal liver from VTM cows • Day 83: ↑ selenium and zinc related genes in fetal liver from MG+VTM cows • Day 83: ↑ mineral absorption pathway in fetal liver from VTM cows • Day 83: ↓ lipid regulating genes in fetal liver from MG cows	Diniz et al., Animals 13:600	2023	10.3390/ani13040600

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Table 1. (*Continued*)

Underfed (UN) vs Control (CON)	Day 0 (breeding) to 50	Beef cattle, nulliparous	• Day 50: overexpression of biological processes in blood coagulation, immune defense & inflammatory response, and energy metabolism in fetal liver from UN cows • Day 50: overexpression of biological processes in muscle structure and development, myotube & myoblast differentiation in fetal skeletal muscle from UN cows • Day 50: overexpression of biological processes in central nervous system & brain development in fetal cerebrum from UN cows	Diniz et al., Sci. Rep. 11:2771	2021	10.1038/s41598-021-82156-w
High protein (DG) vs Control (CON)	Day 192 to day 118 of lactation	Beef cattle, nulliparous	• Postnatal: ↑ body weights, hip height, plasma urea N in female offspring after weaning from DG cows • Postnatal: ↑ body weight & % mature BW at puberty attainment in female offspring from DG cows • Postnatal: ↑ pregnancy rate to AI in female offspring from DG cows & no differences in dystocia at parturition	Gunn et al., J. Anim. Sci. 93:746-757	2015	10.2527/jas2014-8130
Low gain (LG) vs Moderate gain (MG)	Day 0 (breeding) to 85	Beef cattle, nulliparous	• Birth: ↑ body weights, chest circumference in calves from MG cows but no differences in serum NEFA, glucose, insulin, or IGF-1 in calves • Post-weaning: ↑ body weight, ADG, and eating rate in females from MG cows	Baumgaertner et al., J. Anim. Sci. 102	2024	10.1093/jas/skae193
High protein perintatal (HPeri) vs Low protein perinatal (LPeri) vs High protein early-mid gestation (HPost) vs Low-protein early-mid (LPost)	Day -60 (before breeding) to day 23 of gestation then swapped to opposing nutritional group from day 24 to day 98 of gestation	Beef cattle, nulliparous	• Day 98: ↓ placentome number in LPeri & placentome volume in Lpost • Day 98: ↓ brain weight in fetuses from Lperi • Day 98: ↓ heart, left ventricle, right ventricle weights, and proportional growth in fetuses from Lpost • Day 98: Altered hepatic gene expression by diets and sex • Birth: no differences in gestation length, placenta measures, calf morphometrics, or proportional growth	Copping et al., Reprod. Fertil. Dev. 32:495-507	2020	10.1071/RD19017
Low gain (LG) vs Moderate gain (MG) with Vitamin (VTM) or Without (NoVTM)	Supplement: 148 to 71 days before breeding Diet: Day 0 to 83	Beef cattle, nulliparous	• Day 83: ↑ NEFA & insulin in NoVTM cows • Day 83: ↑ IGF-1, P4, CL weight & diameter in MG cows • No differences in allantoic or amniotic fluid glucose or fructose concentration	Menezes et al., Animals., 13(14):1757	2022	10.3390/ani12141757
			• Day 83: alterations in the fetal liver lipidome (metabolites & pathways) mostly in fetuses from LG cows	Menezes et al., Metabolites., 13(2):175	2023	10.3390/metabo13020175
			• Day 83: 17% of amino acid, carbohydrate, and energy metabolism metabolites were altered by Gain X Suppl in fetal liver	Crouse et al., Metabolites., 12(8):696	2022	10.3390/metabo12080696
Restricted nutrition (RES) vs Adequate nutrition (ADQ) with (MEL) or without (CON) melatonin	Day 160 to 240	Beef cattle, nulliparous	• Gestation: ↓ uterine blood flow in RES cows • Day 240: ↓ fetal morphometrics in RES cows • Day 240: ↓ neutral amino acid transporter in COT & CAR, and glucose transporter transcript abundance in CAR from RES cows	Contreras-Correa et al., J. Anim. Sci., 99(9)	2021	10.1093/jas/skab242
			• Day 240: ↓ amino acids in fetal plasma & amnion from RES cows	Swanson et al., Metabolites., 12(12):1208	2022	10.3390/metabo12121208

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Table 1. (*Continued*)

Treatment	Day of gestation	Species and parity	Responses	Reference	Year	doi
Low nutrition (L) vs Moderate nutrition (M)	Day 32 to 115 then realimented to common CON diet	Beef cattle, nulliparous	• Postnatal: ↑ skeletal muscle DNA & fiber area, liver protein, and pancreas DNA in castrated male offspring from L cows • Postnatal: ↓ AP2, CD36, & GLUT4 transcript abundance in perirenal fat from castrated male offspring from L cows	Long et al., J. Anim. Sci., 88(10):3251-3261	2010	10.2527/jas.2009-2512
Vitamin and mineral supplement (VTM) vs Basal diet (CON)	Day 0 to parturition	Beef cattle, nulliparous	• Birth: ↑ colostrum volume, weight, and mineral in VTM cows • Birth: ↑ liver minerals in offspring from VTM & Se in COT • Postnatal: ↑ pre-weaning body weight & post-weaning chest and abdominal circumferences in offspring from VTM cows • Postnatal: ↑ glucose at birth & ↓ BUN at weaning and breeding in offspring from VTM cows	Hurlbert et al., J. Anim. Sci., 102	2024	10.1093/jas.skae002
Nutrient restriction (RES) vs Control (CON) with one-carbon metabolite supplement (+OCM) or without (-OCM)	Day 0 to 63	Beef cattle, nulliparous	• Day 63: ↑ 5-methyl THF in allantoic & amniotic fluid from +OCM cows • Day 63: no differences in fetal liver in one-carbon metabolism metabolites & cofactors (Diet by Suppl)	Syring et al., J. Anim. Sci., 102	2024	10.1093/jas/skae202
			• Day 63: fetal liver amino acid, carbohydrate, energy, & vitamins and cofactors pathways were enriched in Diet by Suppl metabolomic analysis	Safain et al., J. Anim. Sci., 102	2024	10.1093/jas/skae258
			• Day 161: ↓ small intestine weight in fetuses from +OCM cows • Day 161: ↓ small intestine villi capillary area density & crypt VEGFR2 in fetuses from RES cows	Daneshi et al., Vet. Sci., 11(4)	2024	10.3390/vetsci11040146
Nutrient restricted (RES) vs Control (CON)	Day 0 to 50	Beef cattle, nulliparous	• Day 50: ↓ INFτ transcript abundance in RES caruncle tissue & circulating progesterone • Day 16: ↑ INFτ transcript abundance in RES fetal membranes	McLean et al., J. Anim. Sci., 96(3):950-963	2018	10.1093/jas/skx001
			• Day 50: functional categories from DEG in fetal liver from RES vs CON cows are metabolic pathways, protein kinase, nucleosome core, mRNA splicing & complement/coagulation • Day 50: functional categories from DEG in fetal skeletal muscle from RES vs CON cows are skeletal muscle, embryogenesis & signaling cascade	Crouse et al., Transl. Anim. Sci., 3:855-866	2019	10.1093/tas/txz026
			• Day 50: ↑ vitamin B_{12} in allantoic fluid from RES cows • Day 50: ↓ DHFR & ↑ PRMT7 transcript abundance in fetal liver from RES cows	Syring et al., J. Anim. Sci., 101	2023	10.1093/jas/skad139
High energy (H) vs Low energy (L)	100 days prepartum (~day 185 of gestation to parturition) Exp 2. 100 to 30 days prepartum all cows were fed L then L vs H the final 30 days until parturition	Beef cattle, primiparous	• Postnatal: ↓ birth & weaning weights, neonatal survival in calves from L cows 100 days prepartum • Exp 2. Postnatal: 10% stillbirths & 19% death loss from scours in calves from continuously L cows (33% of calves from H cows had scours but death loss was 0%)	Corah et al., J. Anim. Sci. 41:3	1975	10.2527/jas1975.413819x
Low starch (LS) vs High starch (HS)	Day 135 to 271	Beef cattle, multiparous	• Birth: ↑ transcript abundance of H19, IGF2R, MEG8, and DMNT3a in offspring skeletal muscle from HS cows	Wang et al., J. Anim. Sci. 93:35-40	2015	10.2527/jas2014-8148

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Table 1. (*Continued*)

Underfed (UN) vs Control (CON)	Day 0 (breeding) to 83	Beef cattle, multiparous	• Postnatal: ↓ in female offspring from UN cows at weaning but no differences at first breeding (16 months of age) • Postnatal: ↑ medium follicles at 9.5 mos of age and large follicles at 15 mos of age in females from UN cows Postnatal: ↑ NEFA & cholesterol in females from UN cows at 15 mos of age	Noya et al., Animals 9:1072	2019	10.3390/ani9121072
Overfed (HIGH) vs Underfed (LOW)	Day 147 to 247	Beef cattle, multiparous	• Day 247: ↑ IGF1 & ↑ IGF1R transcript abundance in fetal liver from HIGH cows • Day 247: ↑ IGF1, IGF1R, INSR, MYOD1, MYOG & PPARG transcript abundance in fetal skeletal muscle from LOW cows • Day 247: Skeletal muscle expression of IGF1, IGF1R, IGF2, IGF2R, MYOG & SRF were negatively correlated with fetal body weight • Day 247: ↓ skeletal muscle miR-1 & miR-133a in fetuses from LOW cows • Day 247: ↑ skeletal muscle IGF2 DMR2 DNA methylation in fetuses from HIGH cows	Paradis et al., BMC Genomics., 18:632	2017	10.1186/s12864-017-4051-5
Nutrient restricted (NR) vs Control (CON)	Day 0 to 125 then common CON diet until day 245	Beef cattle, multiparous	• Day 125: ↓ glucose & morphometrics in fetuses from NR cows classified as IUGR • Day 125: ↓ allantoic fluid volume in NR cows • Day 245: no differences in fetal morphometrics	Long et al., J. Anim. Sci., 97(6):1950-1959	2009	10.2527/jas.2008-1672
Methionine supplement (M) vs Control (C)	30 days before conception to day 90	Beef cattle, multiparous	• Postnatal: gene-sets enrichment analysis in male offspring skeletal muscle from M vs C cows showed biological functions in muscle development & physiology, ATP activities, RNA splicing, postsynaptic membrane activities, adherens junctions & actin cytoskeleton, and ion binding & transportation • Postnatal: 214,676 cytosines were differentially methylated in male offspring skeletal muscle from M vs C cows	Liu et al., BMC Genomics., 22(780)	2021	10.1186/s12864-021-08065-4
Adequate selenium (CON) vs Supranutritional selenium (SSe)	Trimester 1, 2, or 3 of gestation	Beef cattle, multiparous	• Birth: ↑ circulating Se in offspring from trimester 1, 2, and 3 SSe cows • Birth: ↑ skeletal muscle selenium in offspring from trimester 3 SSe cows • Birth: ↑ energy homeostasis, transcription/translation, & muscle development in offspring skeletal muscle from differing trimester SSe cows • Birth: ↓ adaptive immunity, metabolic pathways, muscle development & small molecule metabolism in offspring skeletal muscle from differing trimester SSe cows	Diniz et al., Genes., 12(12):1884	2021	10.3390/genes12121884
Nutrient restriction (NR) vs control (CON)	Day 30 to 125	Beef cattle, multiparous	• Day 125: ↓ CAR & COT weights in NR cows • Day 250: ↓ weight, capillary area, surface, & number density in COT from NR cows	Vonnahme et al., J. Anim. Sci., 85(10):2464-2472	2007	10.2527/jas.2006-805
Overfed (OVE) vs Control (CON)	Day 21 prepartum to parturition	Dairy cattle, multiparous	• Parturition: No differences in gestation length, colostrum IgG, calf birth weights or IgG absorption	Osorio et al., J. Dairy Sci. 96:3573-3587	2013	10.38/jds.2012-5759

(*Continued*)

Table 1. (*Continued*)

Treatment	Day of gestation	Species and parity	Responses	Reference	Year	doi
			• Parturition: ↑ glucose metabolite was in OVE calves after colostrum consumption compared with CON • Parturition: No differences in growth hormones, immune, stress, or oxidative stress markers, phagocytosis or inflammatory and oxidative stress genes in calves before or after colostrum intake			
Methionine supplement (MET) vs Control (CON)	28 days before parturition	Dairy cattle, multiparou	• Postnatal: ↑ DMI in MET cows & male calf birth weights • Postnatal: ↑ body weight & length, hip & wither height & starter grain intake in male & female calves from MET cows • Parturition: ↑ isocitrate acid, NAD/NAD(H), cysteinesulfinic acid, glutathione & vitamin B_{12} metabolites in MET placenta with male calves • Parturition: ↑ methionine & SAM metabolites in MET placenta with female calves • Parturition: ↑ DNMT3A & DMNT3B transcript abundance in MET placenta with female fetuses but no differences in placentas with male fetuses	Batistel et al., J. Nutr., 149:6-17	2019	10.1093/jn/nxy240

Accordingly, they will continue to provide a dual purpose with a dual-benefit approach to addressing critical questions in agricultural and biomedical sciences.[14,15] The journal "*Animal Frontiers*" has dedicated two entire issues on developmental programming and farm animals as biomedical models ("*Developmental programming: What mom eats matters!*," Volume 7, Issue 3, July 2017[16]; and "*Farm animals are important biomedical models*, Volume 9, Issue 3, July 2019" which presents a collection of reviews on that very topic[17]). Specifically, the use of livestock models of maternal nutrition in developmental programming paradigms has contributed significantly to the field by leveraging insights into both agricultural production practices and human biomedicine.

A detailed presentation of all aspects of nutrition and developmental programming in livestock is beyond the scope of this review; however, several excellent reviews[4,5,8,9,18–20] and several journal article collections (*Animal Frontiers, "Developmental programming: What Mom eats Matters,"*[16]; *Veterinary Clinics of North America, Food Animal Practice, Developmental Programming in Livestock Production,"*[21]; and *Frontiers in Genetics, "Genomic Basis of Developmental Programming in Livestock, Insights into Nutrition, Health, and Production"*[22]) have been published recently, and readers are referred to those publications for additional information and discussion.

Livestock models of developmental programming include global nutrition (i.e., over- or under-nutrition) and specific macronutrient and micronutrient excess or deficiency. In addition, strategic supplementation of nutrients has been successful in mitigating these negative consequences of developmental programming in both humans[23] and livestock.[24–27] These models have also focused on differing periods, or "windows," of fetal/offspring development, which is logical as tissues and systems develop at different rates and times during gestation and postnatally.[18,19,28–30] Most studies have investigated the effects of maternal nutrition on developmental programming during mid and late gestation rather than early gestation; however, the periconceptional period and very early gestation are likely critical windows of susceptibility to long-term developmental programming events.[18] Taken together, the preponderance of data indicates that developmental programming affects multiple organ systems, transcription of many genes, epigenetic landscape, metabolic outcomes, production and performance measures, and health and longevity of the offspring.[9,10,13,19,30,31] Emerging data with livestock models have confirmed that some effects of developmental programming can be multigenerational.[4,5,9,13,18–20,32]

Though there are extensive data regarding the contributions of maternal nutrition on the developing offspring, the body of evidence regarding the contributions of sire nutrition during spermatogenesis is also growing (see summary in Table 2). The mode of action of paternal programming is likely through alterations in sperm miRNA, DNA methylation, histone modifications, oxidative stress/DNA damage, cytokine response, and/or seminal microbiome that subsequently impacts the embryo directly at conception or indirectly via the female immune response.[30,33] Feedstuffs providing substrates for epigenetic processes (methionine, folic acid, and other methyl donors) have been shown to affect embryo transcript abundance, DNA methylation, embryo production and epigenetic properties, and offspring phenotypes in swine, sheep, and cattle models.[34–38] In addition, models of dietary alteration in polyunsaturated fatty acids have resulted in differences in embryo lipid content and gene expression in cattle.[39,40] Managing bulls for an increased rate of gain also reduced the proportion of embryos that reached the blastocyst stage of

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Table 2. Summary of livestock paternal nutrition models demonstrating paternal programming effects on embryos and offspring[1]

Species	Paternal Diet	Effects in embryos/offspring	Reference	Year	doi
Cattle	Diets containing omega 3 (fish oil or flax oil) vs saturated fat control	Enhanced blastocyst rate and altered gene expression of blastocysts from omega 3 group	Kalo *et al.*, PLoS ONE., 17(3)	2022	10.1371/journal.pone.0265650
Cattle	Diets containing 200 mg/d poly unsaturated fatty acids from 14 to 24 months of age	Poly unsaturated fatty acids reduced sperm motility, altered lipid content, and increased acrosome damage in sperm, and accumulation of lipids in blastocysts	Bastos *et al.*, Theriogenology., 175	2021	10.1016/j.theriogenology.2021.08.031
Cattle	Maintenance or High gain (1.38 kg/d)	High gain reduced the proportion of cleaved oocytes continuing to blastocyst stage but did not influence the expression of the 6 genes evaluated	Seekford *et al.*, Reproduction., 166(2)	2023	10.1530/rep-23-0006
Sheep	Pre-pubertal methionine vs control	Prepubertal diet influenced sperm methylation and gene expression of embryos. High correlation between some differentially methylated cytosines and differentially expressed genes	Townsend *et al.*, Environ Epigenet., 9(1)	2023	10.1093/eep/dvac029
Sheep	Pre-pubertal methionine vs control	Male offspring (F1) from rams receiving methionine had decreased body weight and scrotal circumference at puberty	Gross *et al.*, Front Genet., 11:597943	2020	10.3389/fgene.2020.597943
Sheep	Pre-pubertal methionine vs control; evaluation of F2 and F3 generations	Scrotal circumference, phenotype, and altered methylation patterns were observed in sperm of F1, F2, and F3 generations	Braz *et al.*, PNAS Nexus., 1(2)	2022	10.1093/pnasnexus/pgac040
Sheep	Pre-pubertal methionine vs control	Identified genes in genomic regions of F1 and F2 offspring that escape epigenetic reprogramming	Braz *et al.*, Environ Epigenet., 10(1)	2024	10.1093/eep/dvad010
Sheep	Positive, maintenance, or negative plane of pre-breeding nutrition	Rams on negative plane of pre-breeding nutrition had offspring with greater birth weights and morphometric measures than positive and maintenance.	Bochantin-Winders *et al.*, J Anim Sci.	2024	10.1093/jas/skae207
Sheep	Ewe lambs from sires managed on positive, maintenance, or negative plane of pre-breeding nutrition	Ewe lambs from negative plane of pre-breeding nutrition sires had greater average daily gain than those from positive sires. Lambs from negative sires tended to have greater concentrations of IGF-1 than lambs from positive and maintenance sires. Sire nutrition influenced insulin AUC and ratio of insulin: glucose after an in vivo glucose tolerance test	Bochantin-Winders *et al.*, J Anim Sci.	2024	10.1093/jas/skae301
Swine	Methyl donors vs no methyl donors	Differential gene expression and DNA methylation and altered back fat	Braunschweig *et al.*, PLoS ONE., 159(5)	2012	10.1371/journal.pone.0030583

[1]Adapted from Dahlen *et al.*, 2023 and Dahlen *et al.*, 2024.
IGF-1, insulin like growth factor 1.

development,[41] and models providing a common diet to rams and managing for either weight loss, maintenance, or gain resulted in alterations in lamb birth weight, daily gain, and metabolic response to a glucose challenge.[42,43]

Placental function and developmental programming

Several reviews have been published examining the role of the placenta in developmental programming,[2,31,44–47] and the reader is referred to these for further details. Suffice it to say that there is strong evidence supporting placental development, especially vascular development and blood flow, which are major factors in developmental programming of fetuses, and therefore, in offspring development, health, productivity, and longevity. For example, in every model of pregnancy in which fetal and/or placental growth are compromised, as reflected by their weights, placental vascular development and blood flow are also affected. These models include overfed adolescents, underfed adolescents and adults, multiple fetuses, maternal genotype, maternal age, maternal heat stress, and assisted reproductive techniques (Table 3). In addition, in several models in which fetal or placental weights are unaffected (underfed adult cows, vitamin-mineral supplementation, one-carbon metabolite supplementation, and maternal exercise), placental vascular development or blood flows exhibit compensatory increases (Table 3). This latter observation implies not only that the placenta is capable of compensatory responses to maternal stressors, as we and others have argued before,[9] but also that developmental programming responses can indeed be adaptive.

Programming of gene expression and epigenetic landscape

The interplay between genetics and environment is central to a long-standing nature versus nurture debate. However, epigenetics

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Table 3. Fetal and placental weights (see footnote about stage of gestation[1]), placental vascularity and placental (gravid uterine[§] or umbilical[‡]) blood flows in various models of maternal stress in livestock

Model	Species	Fetal weight	Placental weight	Placental vascularity	Gravid uterine[§] or umbilical[‡] blood flow
Overfed Adolescent	Sheep	−20 to −40%	−20 to −45%	−31%	−36[§] to −37%[‡]
Underfed Adolescent	Sheep	−17%	NS	−18%	—
Underfed Adult	Sheep Cow	−9 to −12% NS	— −34%	−14% +40%	−25%[§§] or NS[‡] —
Protein Supplementation	Cow	+ 12%	—	—	—
Vitamin-Mineral Supplementation	Cow	NS	—	+ 47%	—
One-carbon metabolite supplementation	Cow	—	—	+ 28%	—
Heat Stress	Sheep Cow	−42% −42%	−51% —	— —	−26[§§]to −60%[‡] −30[§] to −28%[‡]
Exercise	Pig	NS	NS	—	+ 18%[‡]
Multiple Pregnancy	Sheep	−30%	−37%	−30%	−23%[§§]
Maternal Genotype	Sheep	−44 to 54%	−28%	−33%	—
Adolescent vs, Adult	Sheep	−16%	−26%	−24%	—
Assisted Reproduction	Sheep	—	—	−63-85	—

[1]For sheep, samples were collected on day 130–135 (0.87–0.90) of gestation, except for Assisted Reproduction, which were collected on day 22 (0.15) of gestation; for cows, samples collected on day 63 (0.22; one-carbon metabolite supplementation) or 250 (0.89; undernutrition) of gestation or at parturition (vitamin-mineral supplementation); for pigs, samples collected on day 94 to 104 of gestation. Table adapted from Reynolds *et al.*, 2023; https://doi.org/10.1016/j.anireprosci.2023.107322).
NS, not significant $P > 0.05$.

has provided a new perspective to this debate, the mechanism to explain the origins of developmental programming or the DOHaD hypothesis, and new paradigms on genetic inheritance.[48] Epigenetics has been defined as molecular factors and processes that can affect genome activity and gene expression without changes in the DNA sequence.[49] Environmental factors, such as parental nutrition, can potentially leave epigenetic marks, or epimutations, that can be inherited through subsequent developmental stages and likely across generations. Epigenetic modulation of gene expression is likely the mechanism through which nutrient supply programs fetal development.[10,50–52] However, the mechanisms, extent, and potential for transmitting epigenetic information across generations remain unclear. Based on our current knowledge, epigenetic marks are established during gametogenesis, including DNA methylation, non-coding RNAs (ncRNAs), and histone modifications.[53–56] These mechanisms can regulate gene expression at the transcriptional level via DNA methylation and/or histone modifications and the translational level via ncRNAs.[54] DNA methyltransferases (DNMTs) are key enzymes involved with maintenance and *de novo* DNA methylation.[53] It is important to note that during fertilization, germ cells deliver not only their haploid genomes but also their epigenomes, which contain codes for pre- and post-implantation reprogramming and embryonic development.[54] This is of particular importance in the realm of developing programming, considering the parental epigenome will be transferred to their offspring. In fact, females' oocytes will be developed and fixed *in utero*, therefore postnatal recovery or alterations are not possible. As such, it is likely negative alterations in the epigenome will likely be transgenerational.

Nutrients can interact directly with the genome through nutrient-sensing signaling pathways and nutrient-dependent genes or indirectly via epigenetic mechanisms. Epigenetic signatures in somatic tissues can be changed through enzymes that add or remove "epigenetic tags" to or from DNA and histones.[53,54] Our previous review of the molecular mechanisms and tissue adaptation in developmental programming discusses these interactions.[10] In-depth reviews on the effects of specific nutrients, such as minerals and one-carbon metabolites, have also been published.[37,57–61] Mounting evidence has highlighted differential gene regulation and expression of the brain, liver, and muscle in the offspring in response to *in utero* nutrition.[62–65] We previously reported that nutrient restriction from breeding to day 50 of gestation affected the expression of fetal hepatic genes, including members of the histone H1, H2A, H2B, and H4 families.[63] The 13 differentially expressed histone-modifying genes included those associated with acetylation and de-acetylation, methylation, phosphorylation, and ubiquitination. Interestingly, in skeletal muscle, we reported that the rewiring of major regulators likely modulates the expression of gene targets as an adaptive response to nutrient availability, affecting tissue development. For example, the myogenic regulatory factors *MYOD1*, *MYF5*, and *MYOG* were negatively and differentially correlated with *ZBTB33* and/or *ZNF131* transcription factors in nutrient-restricted fetuses, likely negatively affecting myogenesis.[64] These findings are relevant to human health and wellbeing because of the widespread malnutrition that still exists among the population, which is contributing to the programming of future generations as discussed previously. Furthermore, these nutritional impacts on skeletal muscle are of concern when considering both human and animal skeletal muscle in the landscape of overall health and wellbeing among the population, which is discussed in further detail within this review.

Most of the epigenomic studies related to fetal programming have focused on the F1 generation. Maternal nutrient restriction during an 84-d period of mid-gestation did not affect growth or development in beef cattle.[66] On the other hand, at weaning and in early adolescence, the expression of micro-RNAs (miRNAs) previously associated with the growth and/or development of skeletal muscle and/or adipose tissue was affected by the *in utero* environment.[66] Research in sheep has shown that under-nutrition 60

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days before to 6 days after conception programs changes in insulin-signaling molecules and the expression of miRNAs in skeletal muscle and liver during late gestation (days 136–138).[67,68] Transcriptional and post-transcriptional gene silencing is modulated by miRNAs through specific base pairing with target genes.[69] Developmental and physiological processes, including myogenesis, also are modulated by miRNAs.[70] Furthermore, miRNAs can modulate the function of components of the epigenetic machinery, interacting to form a complex, bi-directional regulatory circuit that regulates gene expression.[48] Interestingly, in humans and mice, it has been shown that miRNAs can be trans-placentally transmitted from the mother to the fetus.[71] However, we still have a paucity of knowledge regarding mechanisms by which miRNA modulates gene expression in livestock models and its impacts on health and wellbeing.

DNA methylation is one of the most studied epigenetic mechanisms. Most of the evidence of programming through DNA methylation is related to exposure to toxicants and maternal nutritional changes.[48,49,72] Maternal supplementation with epigenetic modifiers (e.g., methionine, choline, folate, and vitamin B_{12}) has been examined because of their roles as methyl donors or cofactors in methylation reactions.[73] Supplementation of choline to bovine embryos during *in vitro* fertilization resulted in a tendency for positive effects at birth and improved weaning weights.[74] These authors also reported differential methylation of genes involved with the mTOR signaling pathway, a key regulator of muscle development. Interestingly, maternal methionine supplementation during the periconceptual period through the completion of the first trimester of gestation led to persistent methylation differences over time in beef calves.[58] Moreover, methionine supply during mid-gestation affected the expression and activity of placental nutrient transporters in a sex-dependent manner and upregulated placental mTOR and phosphorylated mTOR; however, changes in DNA methylation were not investigated. While these studies demonstrate DNA methylation is involved in developmental programming, its long term effects on growth, metabolism, and health and wellbeing are largely unexplored.

In sheep, Peterson *et al.* (2021)[59] examined the effects of maternal under- and over-nutrition during gestation on offspring pancreas development and DNA methylation. They reported differential DNA methylation in fetal pancreas collected at days 90 or 135 of gestation or within 24 h of birth. Their findings suggest that DNA methylation patterns are diet- and sex-dependent. These results indicate that maternal nutrition during gestation significantly affects fetal epigenetic programming and gene expression. Furthermore, supplementation with key nutrients, such as choline and methionine, positively affects growth and performance[74] and can have long-term effects on growth and metabolic efficiency.[58,75]

There is a paucity of information related to the effects and mechanisms of intergenerational inheritance of epigenetic marks in livestock. This has been primarily influenced by limited data suggesting that parental nutrition, either prior to or during pregnancy, can affect growth and carcass traits in food-producing livestock.[10] Additionally, the literature suggests there might be a lag time from "insult" to observable effects in offspring performance.[30] Thus, as animals are slaughtered for human consumption, it is possible that long-term developmental programming effects may not have had enough time to manifest in livestock. However, some studies have shown transgenerational epigenetic inheritance in livestock. Braunschweig *et al.*,[35]investigated the effect of a paternal, methyl donor-enriched diet on subsequent generations. They reported significant changes in subcutaneous adipose, gene expression, and DNA methylation in the experimental compared with the control group.[35]

Similarly, Braz *et al.*,[37] reported 107 differentially methylated cytosines (DMCs) that were common between the F1 and F2 generations when F0 rams were supplemented with methionine from weaning to puberty. The authors reported that most long-term phenotypic negative effects were observed in the F2 generation. In F2 females, weaning and postweaning body weights were negatively affected by the paternal diet. Similar negative effects were observed in the F2 male's loin muscle depth. Furthermore, the paternal diet reduced the testicular size in both F1 and F2 generations compared with the control group.[37] In a follow-up study of the same experimental population, the authors reported that the DMCs were found in transposable elements, non-repetitive regions, and both imprinted and non-imprinted genes. They suggested that some genomic regions could escape reprogramming and serve as potential candidates for transgenerational epigenetic inheritance. New knowledge is needed to better understand long-term impacts for biomedicine, and transgenerational impacts for biomedicine and the production of animal products for human consumption.

In addition to the mechanisms described above, growing evidence suggests the role of the maternal microbiota in fetal developmental programming. However, the mechanisms underlying the regulation of the maternal and fetal microbiomes and their effects on fetal genome programming are yet to be determined. Data from beef cattle indicate that colonization with pioneer microbiota may occur during early gestation in bovine fetuses and that the maternal nutritional regime during gestation may influence the early fetal microbiota.[77] Preclinical studies in mice have revealed the effects of the maternal microbiome on prenatal development through the transfer of microbial metabolites,[78] which affected fetal metabolism, immunity, and neurodevelopment.[79,80] Gustafson *et al.*,[81] showed that the maternal gut microbiome affected the neurodevelopment, behavior, and body weight of the offspring in mice. They showed differences in hippocampal gene expression within differentially methylated regions and in genes underlying pathways associated with growth and feeding behavior. Further research, however, is still needed using livestock models to determine the effects and extent of maternal microbiomes on colonizing and programming the offspring.

With the development and refinement of methods and cost effectiveness to explore gene expression and the epigenetic landscape, it has become a rapidly evolving field of study. As such, emerging data suggests its role in developmental programming, particularly concerning trans-generational impacts. Nevertheless, we look to future findings to confirm these initial findings.

Programming of key metabolic tissues

Maintenance energy use is likely susceptible to developmental programming *in utero*.[11,82] In general, nutrient demand follows energy demand and energetic efficiency often reflects the overall efficiency of nutrient use. Tissue metabolic rate affects the rate of nutrient use. Consequently, more metabolically active tissues consume greater proportions of nutrients compared with less metabolically active tissues on a per unit of tissue basis. Specifically, in cattle, the portal drained viscera consume approximately 40% of maintenance energy demands but represent a comparatively small proportion of overall body weight. Within the viscera, the liver and

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intestinal tissues each consume approximately half of the 40%. Conversely, skeletal muscle represents a large portion of overall body weight and is metabolically active but consumes between 20 and 25% of maintenance energy. These concepts are relevant because small changes in nutrient energy use for maintenance can shift energy (and other nutrients) toward product formation and improve production efficiencies. In addition, metabolically active tissues appear to be responsive to nutritional planes,[83,84] and consequently may be programmed by inappropriate maternal nutrition during gestation.

Programming of visceral tissues

Visceral tissues are responsive to nutritional plane.[85–87] Likewise, in ruminant livestock, differing nutritional planes during gestation can have large impacts on maternal visceral tissues, including the liver and intestine.[88–91] As discussed below, the data also indicate that maternal plane of nutrition during gestation can influence visceral tissues of the offspring both pre- and post-natal.

Offspring liver

Proper liver function is critical for efficient metabolic function, particularly concerning glucose, which is a key nutrient for skeletal muscle growth. Data from a sheep model of compromised maternal nutrition and developmental programming of offspring[92,93] demonstrated that liver oxygen consumption at both d 130 of gestation and d 54 postnatal is reduced in offspring from nutrient-restricted compared with control fed dams. In beef heifers subjected to maternal nutrient restriction during pregnancy, Safain *et al.*,[94] showed that mitochondrial respiration rates from d 161 fetuses were increased in response to dietary supplementation with methionine, choline, folate and vitamin B_{12} from d 0 to 63 of gestation. Their work agrees with earlier data[73] showing that mitochondrial respiration was responsive to both planes of nutrition and one-carbon metabolite supplementation in a bovine cell culture model.

Fetal hepatic transcript abundance was also influenced by maternal nutritional intake during early pregnancy,[63] with pathway analysis demonstrating changes in gene expression of energy, amino acids, carbohydrates, and other metabolic pathways. Research[24,27,95] has investigated the influence of moderate nutrient restriction of beef heifers during early gestation on metabolomic profiles in fetal liver. Their work demonstrates that changes in maternal nutrition during early gestation can alter fetal hepatic gene expression and metabolic profiles within multiple pathways, including carbohydrate, amino acid, and energy metabolism. However, research is lacking regarding the postnatal implications of altered fetal liver metabolism on growth, efficiency and health outcomes in the offspring.

Offspring small intestine

Healthy offspring intestinal tissues are essential to neonatal survival and growth. Consequently, understanding the development and potential programming of these tissues by compromised maternal nutrition should inform management decisions and improve offspring outcomes and growth efficiencies. As shown in Table 4, research over the past decade demonstrates that both pre- and post-natal intestinal tissues are responsive to maternal plane of nutrition and appear to be functionally programmed postnatally.[96–99] Specifically, fetuses from nutrient restricted sheep had reduced small intestine vasculature, protein concentration, protein to DNA ratio, and oxygen consumption.[89,93] Similarly, fetuses from nutrient restricted cows that were realimented had increased small intestine vascularity but decreased VEGFR2 in crypts, and decreased crypt cell proliferation.[26,96] Moreover, lambs born from nutrient restricted ewes had decreased small intestine capillary surface density and size, total vascularity, cell proliferation, and weight.[96,97,99] Whereas lambs born from overnourished ewes had increased small intestine DNA content but reduced cell proliferation.[96,99] Interestingly, recent work in a heifer model of cross-generational developmental programming has demonstrated that F2 offspring exhibit altered gene expression and morphometrics in jejunal tissues.[32,100,101] Detailed investigation of intestinal function and health as affected by maternal stress, particularly nutritional stress, during critical windows of development will increase our understanding of both maternal and offspring management.

Offspring skeletal muscle

Proper skeletal muscle development *in utero* and subsequent growth postnatally is important for human development. In addition, livestock skeletal muscle is an important end-product of production agriculture, providing high-quality protein and essential micronutrients to the human diet. In humans, skeletal muscle mass is important to physical health, including weight management, insulin responsiveness, disease prevention, and longevity.[102–104] Additionally, proper skeletal muscle development *in utero* is critical in livestock and humans because skeletal muscle fiber number in mammals is fixed at birth, and thus skeletal muscle growth postnatally can occur only through hypertrophy of the existing fibers.[105,106] Consequently, if poor maternal nutrition during gestation, and even in the periconceptual period, negatively affects the development of skeletal muscle fibers, it will result in poor skeletal muscle metabolic efficiency in livestock and humans alike. This will ultimately reduce the economic and environmental sustainability of production agriculture and increase the incidence of nutritional, including non-communicable, diseases in humans.[64,105,107–111] The negative effects of poor maternal nutrition on offspring skeletal muscle mass and function have been previously reviewed by Caton *et al.* (2024).[5]

In livestock, maternal undernutrition occurs during seasonal changes in forage quality and quantity, extreme or abnormal weather events, and breeding young females that have yet to reach maturity.[11,112,113] In humans, food insecurity remains a critical issue globally (2.4 billion people in 2022), and within the United States (18 million households in 2023).[114,115] Maternal undernutrition throughout gestation has severe consequences for skeletal muscle development *in utero* and, thus for hypertrophy and metabolic function postnatally. Specifically, skeletal muscle satellite cells derived from offspring subjected to maternal undernutrition had increased myogenic regulatory factors, MyoD and myogenin, from birth through the juvenile stage, but reduced myoblast fusion in the juvenile stage.[116] Offspring from undernourished pregnancies had decreased skeletal muscle fibers, primary to secondary fiber ratio, and increased transcript abundance of ATP binding and protein binding factors.[110]

Additionally, mature offspring from nutrient-restricted pregnancies had reduced type IIa fibers and carnitine palmitoyltransferase-1 activity, increased type IIb fibers, increased intramuscular triglyceride content and altered protein content.[107] Furthermore, individual muscle weights and myosin heavy chain (MHC)-fast fibers were decreased but MHC-slow fibers were increased in offspring from nutrient-restricted pregnancies.[117] In

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Table 4. Summary of effects of maternal nutrition on ruminant offspring small intestine (SI) from selected studies

Species	Gestational Treatments	Age measured[1]	SI mass	Additional SI responses	Reference	Year	doi
Cattle	CON vs RES (d 30 to 125)	d 125 gestation	NS	↑ proliferation in RES	Meyer *et al.*, J Anim Sci., 88	2010	10.2527/jas.2009-2220
Cattle	CON vs RES (d 0 to d 63)	d 161 gestation	NS	↓ VEGFR2 presence in crypts in RES ↓ crypt cell proliferation in RES	Daneshi *et al.*, Vet Sci., 11(4)	2024	10.3390/vetsci11040146
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.*, J Anim Sci., 88	2010	10.2527/jas.2009-2220
Cattle	CON vs RES vs RES + AA supplement (d 45 to 185)	~450 d postnatal	NS	↑ GUCY1B3 mRNA in RES + AA	Meyer *et al.*, J Anim Sci., 85	2007	10.2527/jas.2014-7646
Cattle	CON vs RES (d 0 to d 84)	F2 offspring postnatal	NS	↑ jejunal gene expression in RES	Baumgaertner et al., J Anim Sci., 102	2024	10.1093/jas/skae295
Sheep	CON vs RES (d 50 to 130)	d 130 gestation	NS	↓ protein concentration in RES ↑ oxygen consumption in RES	Prezotto *et al.*, J Anim Physiol Anim Nutr., 98	2014	10.1111/jpn.12142
Sheep	CON vs RES (d 64 to 135)	d 135 gestation	↓ in RES	↓ total vascularity in RES ↓ protein:DNA in RES ↓ GUCY1B3 mRNA in RES	Reed *et al.*, J Anim Sci., 85; Neville *et al.*, J Anim Sci., 88	2007 2010	10.2527/jas.2006-785 10.2527/jas.2009-2706
Sheep	CON vs RES (d 40 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	Meyer *et al.*, J Anim Sci., 88 Meyer *et al.*, J Anim Sci., 91	2010 2013	10.2527/jas.2009-2435 10.2527/jas.2012-5953
Sheep	CON vs OVR (d 40 to birth)	d 20 postnatal	NS	↑ DNA concentration in OVR	Meyer *et al.*, J Anim Sci., 88 Meyer *et al.*, J Anim Sci., 91	2010 2013	10.2527/jas.2009-2435 10.2527/jas.2012-5953
Sheep	CON vs RES (d 50 to birth)	d 180 postnatal	NS	↓ capillary size in RES ↓ total proliferation in RES ↓ GLP-2 mRNA in RES	Yunusova *et al.*, J Anim Sci., 91	2013	10.2527/jas.2012-5134
Sheep	CON vs OVR (d 50 to birth)	d 180 postnatal	NS	↓ total proliferating cells in OVR	Yunusova *et al.*, J Anim Sci., 91	2013	10.2527/jas.2012-5134

[1]Approximate gestation lengths: cattle = 285 d, sheep = 150 d, CON = control, maintenance diet; 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; VEGFR2 = vascular endothelial growth factor receptor 2.

addition, myofiber number, capillary density, and capillary to myofiber ratio were reduced, and insulin and insulin-like growth factor (IGF-1) receptors and glucose transporter type 4 (GLUT4) were increased in offspring from nutrient-restricted pregnancies.[118] Maternal undernutrition was also associated with altered metabolites in the tricarboxylic acid cycle (TCA), synthesis of bioactive amines, and several other metabolic pathways in offspring skeletal muscle, which persisted even following maternal realimentation.[119] Moreover, maternal undernutrition decreased metabolic markers, metabolites, and the function of mitochondria in offspring skeletal muscle.[120] Finally, maternal nutrient restriction altered gene expression in offspring skeletal muscle, including upregulation of genes associated with contraction, intermediate filaments, actin, myosin, troponin, and calcium-binding, whereas genes associated with microtubules and ATP-binding were downregulated, ultimately altering biological pathways involved in hemostasis, and forebrain and skeletal muscle development.[63,64] These observations indicate that maternal nutrient restriction during gestation negatively affects skeletal muscle growth and development and skeletal muscle metabolic function, reducing metabolic efficiency and ultimately impairing muscle development in livestock as well as metabolic health in humans.

Maternal overnutrition also occurs in livestock but is probably more relevant to humans. In 2018, obesity was at an all-time high in the United States, with approximately 40% of adults of child-bearing age being obese.[121] Globally, the prevalence of overweight and obese adults has increased 4-fold since 1990, with more than 2.5 billion adults (43%) overweight and 890 million (16%) obese in 2022.[122] Maternal overnutrition and obesity affect fetal skeletal muscle growth and development and muscle function in the offspring.

Specifically, skeletal muscle protein content and adipogenic and fibrogenic markers were increased, and collagen deposition was

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decreased in offspring from overnourished pregnancies.[123,124] Skeletal muscle lipid accumulation, follistatin gene expression, cross-sectional area neonatally, and type IIa fibers were increased, but type I fibers and cross-sectional area on juveniles were decreased among offspring from overnourished pregnancies.[125] In addition, the ratio of type I to type II fibers, fiber area, and transcript abundance of insulin receptor isoform b receptors and IGF-1 receptors were increased but glucose transporters were decreased in skeletal muscle of offspring from overnourished pregnancies.[126] Moreover, insulin receptors, IGF-1 receptors, and insulin signaling markers were decreased, but triglyceride content, fatty acid transporters, collagen content, and nuclear factor kappa-light-chain-enhancer of activated *B* cells (NF-κB) signaling were increased in skeletal muscle of offspring from overnourished pregnancies.[127]

Circulating glucose and insulin concentrations were also decreased in offspring from overnourished pregnancies.[128] Similarly, plasma glucose, insulin, IGF-1, insulin receptor phosphorylation, tumor necrosis factor alpha (TNFα), and PPARγ were increased, but Akt and mTOR signaling and fiber density were reduced in skeletal muscle of offspring from overnourished pregnancies.[129] Maternal overnutrition also alters metabolites in offspring skeletal muscle, including those associated with amino acid, peptide, carbohydrate, energy, lipid, and nucleotide metabolic pathways.[130] Furthermore, transcript abundance was altered in pathways associated with adipogenesis, regulation of skeletal muscle growth, differentiation, and atrophy, metabolic processes, and protein transcription factors in skeletal muscle of offspring from overnourished pregnancies.[131] Undeniably, maternal overnutrition during gestation negatively affects offspring skeletal muscle growth and development and metabolic function, which has been demonstrated to span generations.[132] These negative effects impair metabolic efficiency and, ultimately health and well-being of the offspring, which affect not only livestock production but also the incidence of non-communicable diseases in humans.

Dietary guidelines during pregnancy and lactation are well-defined in livestock.[113,133–136] However, nutritional requirements during pregnancy and lactation in women are alarmingly poorly defined.[137,138] Evidence suggests that adequate macronutrient consumption during pregnancy is vital for fetal and postnatal growth and development, and thus for offspring health, with protein being the most important maternal dietary nutrient for skeletal muscle development. Protein deficiency during pregnancy decreases skeletal muscle weight, myofiber cross-sectional area, circulating branched-chain amino acids, and markers of protein synthesis but increases myostatin pathway markers.[139] Additionally, genes associated with oxidative phosphorylation, Kreb's cycle, and fatty acid metabolism were upregulated, whereas genes associated with the cell cycle were downregulated, in skeletal muscle of offspring from pregnancies in which the maternal diet was protein deficient.[140] Furthermore, skeletal muscle mass, myofiber cross-sectional area, primary, secondary, and total myofiber number, DNA, RNA, and protein contents, and creatinine kinase activity were decreased and adipocyte area was increased in skeletal muscle of offspring from protein deficient dams. Overall, protein deficiency during pregnancy negatively affects skeletal muscle growth and development, and function in the offspring.[141,142]

In summary, poor maternal nutrition during pregnancy negatively affects fetal and postnatal skeletal muscle growth and development, and metabolic function. These poor outcomes significantly affect both production efficiency in livestock as well as human health.

Programming of immunological function

The health of neonates is established early in postnatal life, primarily through the transfer of maternal antibodies across the placenta or through ingestion of antibodies via maternal colostrum in the immediate postnatal period.[143] A growing body of evidence suggests that in several species (e.g., primates, rodents, and livestock), insults and stressors to the female during pregnancy can impact several functions of immunity and inflammation in the offspring postnatally.[143–145] Maternal stressors that impose alterations to gene transcription patterns in the fetus during intrauterine development or postnatally during the suckling phase have been linked to an unhealthy phenotype in the offspring that appear later in life, including obesity, type II diabetes, asthma, cardiovascular disease/vascular dysfunction, hypertension, and neurological dysfunction.[143,146–150] Throughout intrauterine development, different windows of cell development promote continuous changes in gene expression and the components of the fetal immune system.[151] Furthermore, the level of immune system maturation *in utero* varies for different species, and the type and duration of maternal insult during gestation can create different responses in the innate and adaptive immune systems in the offspring.[152]

In ruminant livestock species, the syndesmochorial placenta prohibits the transfer of large proteins like immunoglobulins (Ig) from the maternal to fetal blood supply.[153] Neonates ultimately rely on the transfer of Ig, immunologically active cells, leukocytes, lymphocytes, cytokines, and other nutritional components of colostrum postnatally to successfully obtain passive transfer of immunity from the maternal to neonatal systems.[153] Colostrum consumption for newborn ruminants paired with postnatal vaccine administration is imperative for both the innate and adaptive immune responses and subsequent long-term productivity and well-being. Because of the critical nature of colostrum for species in which most immune system maturation occurs postnatally, several studies have documented the influence of maternal nutrition on colostrogenesis, post-partum colostrum quality and yield, and health status of the offspring resulting from nutritional insults on the dam,[154–158] with late-gestation as opposed to early gestation nutrition providing the greatest influence on colostrum production.[159] However, few reports have fully examined the role of maternal nutrition during pregnancy and its effects on the development of the innate and adaptive immune systems in the offspring.

Recent investigations in beef heifers have shown that prenatal vitamin and mineral supplementation from breeding to calving increased colostrum yield and micronutrient content; however, no differences in Ig concentrations in colostrum were detected.[156] Furthermore, calves born to supplemented and non-supplemented dams had similar serum concentrations of Ig 24 h after consuming maternal colostrum. Despite the lack of differences in Ig in colostrum and serum, postnatal responses to vaccination, as reflected by antibody titers for several viral respiratory and diarrheal diseases, were greater at birth through weaning in calves born to vitamin and mineral supplemented dams.[156] These data suggest a programmed response in immune function because of the maternal nutritional environment during gestation. We also investigated the effects of vitamin and mineral supplementation

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and maternal rate of gain in beef heifers during the first 12 weeks of gestation on antibody titer response to vaccination in the offspring but found no differences from birth through weaning.[32]

Others have reported that dietary restriction to 70% of maintenance energy requirements in pregnant beef cows for 40 days before parturition reduced viral (BVD-1) antibody titers in the calves after weaning despite similar management, which suggests that calves born to energy-restricted dams may have a programmed increase in susceptibility to BVD-1 and perhaps other viral diseases during postnatal development.[160] Taken together, the mechanisms by which maternal nutrition "programs" offspring immune responses are unclear; however, late-gestation maternal nutrition, aligning with colostrogenesis (i.e., just before parturition), appears to have a greater influence on programming of the neonatal immune system compared with nutritional insults during early gestation. Despite the similar Ig content in colostrum and in the serum of the calf at 24 h of age, reported by Hurlbert *et al.*,[145] the immune responses in calves through weaning was diminished, warranting future investigation. Perhaps epigenetic changes *in utero* are responsible for this "lag time" from the prenatal insult to the response(s) in the offspring postnatally.[32,156,159] Future studies may benefit from coupling the postnatal immune system and growth efficiency evaluations with investigations on the neonatal genome in order to untangle the complex web of maternal nutrition on programmed immune function in livestock species.

Programming of parturition

Parturition marks the culmination of the complex physiological interactions between the mother and the fetus, which involve a regulated sequence of events in which steroid hormones play a central role.[161] The timing and success of parturition are critical for maternal health and the viability and development of the offspring. The World Health Organization reports that preterm birth affects 11% of pregnancies globally,[162] and it accounts for over 75% of perinatal mortality.[163] In humans, pre-term birth has been linked to developmental programming and long-term effects on cardiovascular, pulmonary, metabolic, and behavioral disease risk.[164–168] Additionally, pre-term birth significantly increases the likelihood of low birth weight, which can result in immediate postnatal consequences and heightened risks of lifelong health challenges.[169] Furthermore, among livestock species, pre-term birth is recognized as a significant contributing factor to annual neonatal losses of 10%-30% for lambs and 6%-16% for calves, representing a substantial loss in agricultural sustainability.[170,171]

While the mechanisms initiating labor are still not fully understood, key factors have emerged, particularly those involved in the activation of the fetal hypothalamic-pituitary-adrenal axis (**HPAA**), which drives cortisol release,[172] along with the roles of the steroid hormones estradiol (E2) and progesterone (P4).[173,174] In ruminants, activation of the HPAA, resulting in a significant surge in fetal cortisol concentrations, determines the timing of parturition before birth.[172,175,176] In contrast, cortisol does not play a prominent role in initiating labor in horses[177] or pigs[178]; while cortisol levels increase toward the end of gestation due to the functional HPAA, labor in these species appears to be primarily driven by maternal factors like prostaglandin release or mechanical signals. Furthermore, a slower increase in cortisol concentration is characteristic of humans,[176,179] where labor initiation involves an interplay of maternal, fetal, and placental signals.[180,181] Ultimately, regarding the initiating signal across species, there is a need to shift from progestogenic to estrogenic dominance, either systemically or at the functional level, and prostaglandin production to promote the myometrial contractions and cervical ripening that allows the expulsion of the fetus. Beyond the importance of fetal cortisol in the initiation of parturition, it also plays a critical role in fetal lung maturation by stimulating surfactant production and cellular differentiation, which is essential for extrauterine survival.[182–184]

The diverse mechanisms that initiate labor across species have made it challenging to reach a clear consensus on the exact triggers of parturition. However, recent studies have highlighted the influence of maternal nutrition before and during pregnancy on timing of delivery,[45,185–188] and neonatal viability, which in most species depends primarily on cortisol-induced lung maturation.[180,182,189] Furthermore, it's important to recognize that maternal and fetal nutrition are distinct processes. Although maternal nutrition is a contributing factor, the fetus's access to nutrients is also significantly affected by placental blood flow and metabolism, umbilical circulation, and the endocrine and hormonal environment. Nonetheless, research has demonstrated that maternal nutrition exerts a significant influence on all of these factors.[169,190–193]

Research in humans has established a connection between maternal nutrition and the timing of delivery, which supports the concept of programming of parturition. It has been shown that inadequate maternal nutrition before and at various stages of pregnancy is linked to preterm birth.[194–197] Although numerous studies have been conducted to understand the effects of maternal nutrition on preterm birth in humans, most have been epidemiological, relying on questionnaires to classify the types of foods mothers consume. For ethical reasons, it is not feasible to subject pregnant women to strictly controlled dietary regimens throughout pregnancy. In contrast, the ewe has emerged as the preferred animal model,[198] allowing for specific nutritional interventions that can be precisely administered.

In a study by Bloomfield *et al.*,[188] a 15% decrease in maternal weight during the period from 61 d before conception until 30 d after conception, with ad libitum feed intake thereafter, resulted in an early increase in fetal adrenocorticotropin hormone (**ACTH**) in all fetuses and elevated cortisol levels in half of the fetuses, ultimately leading to premature birth in all treated ewes. Despite this, fetuses of both undernourished and control groups were born with similar sizes, supporting the idea that maternal and fetal nutrition are distinct.[193] Shockingly, the study also found that although the preterm lambs were born at the normal size, they all died soon after birth, suggesting that their organs did not mature sufficiently to survive extrauterine life and that the rise in cortisol might not be enough for complete lung maturation. In a subsequent study, the same treatment was administered, and maternal blood samples were taken for cortisol and prostaglandin analysis, and to determine changes in the E2/P4 ratio from 126 d (approx. 0.85 of gestation) until delivery.[187] The results demonstrated that cortisol, prostaglandin, and the E2/P4 ratio increased before delivery in a similar pattern in both periconceptionally undernourished and control groups during the initiation of the labor. However, the hormonal changes occurred 7–10 days earlier in the undernourished group, leading to premature birth. Similarly, the provision of a maintenance control diet from the second week of pregnancy does not reverse the effect of maternal undernutrition 60 d prior to and during the first week of a twin pregnancy, as Edwards & McMillen[199] showed. This periconceptional undernutrition stimulates the fetal HPAA and raises the concentration of ACTH in late gestation. Together, these studies have demonstrated that programming of parturition can occur in response to changes

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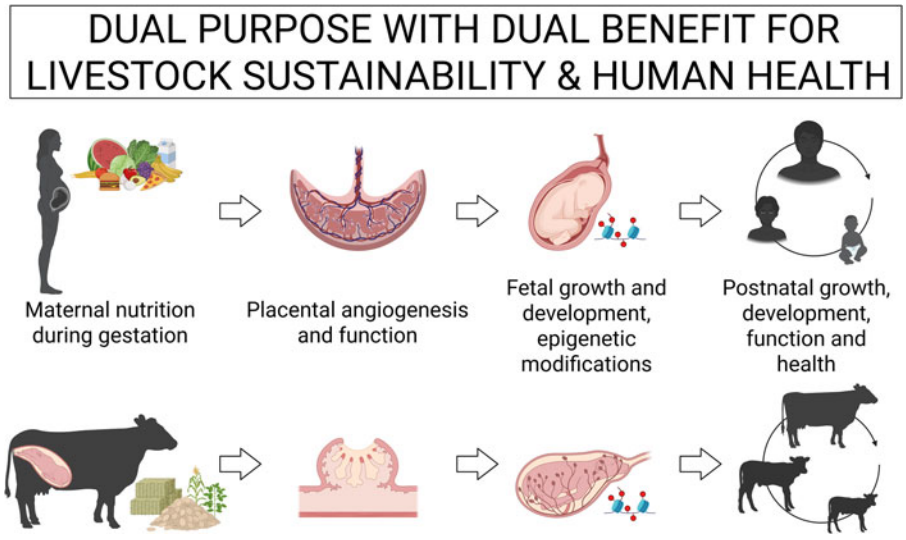


Figure 1. Livestock models of developmental programming positively contribute to human health through translation of research and improving food security.

in maternal periconceptional nutrition, resulting in premature activation of the fetal HPA axis, ultimately leading to preterm birth.

Another study demonstrated a correlation between maternal nutritional status during late gestation and uterine prostaglandin *F* metabolite (**PGFM**) release and timing of delivery.[28] In this study, ewes were nutrient-restricted (but not deprived of water) for 48 h, which led to a significant increase in plasma PGFM levels. The ewes were divided into three groups based on the timing of food withdrawal: before 134 d of gestational age, between 134 and 137 d, and after 137 d. When food was reintroduced or glucose was infused, plasma PGFM levels rapidly returned to baseline. Notably, animals that fasted later in gestation (after 137 d of gestational age) exhibited the greatest plasma PGFM concentrations following fasting. These animals also experienced a decline in plasma P4 during the last 24 h of fasting, but uterine blood flow remained unchanged. Ewes in the late-fasting group gave birth within 12–24 h after the fast ended, a significantly shorter period compared with the other groups.

Similar to the study in ewes, researchers have examined the production of PGFM in pregnant mares with differing dietary states during late gestation.[186] As in sheep, there was an increase in PGFM concentration during fasting, and a rapid decrease in PGFM levels upon refeeding. Thus, nutritional status during late gestation can influence the timing of parturition in ewes and mares by increasing PGFM levels, thereby initiating the onset of labor.

In conclusion, the process of programming parturition and fetal organ maturation is shaped by the interplay between maternal, fetal, placental and environmental factors. Maternal nutrition, both before and during pregnancy, has emerged as an important influence on the timing of labor and neonatal outcomes, as demonstrated particularly in the ewe. Controlled studies in livestock models have revealed that maternal undernutrition can prematurely activate the fetal HPAA, while maternal overnutrition can increase prostaglandin concentrations, both of which can lead to premature delivery. These findings highlight the significance of maternal nutrition not only in determining the timing of parturition but also in shaping the long-term health and viability of the offspring.

Conclusions

Implications of livestock models for other species

Livestock species are particularly advantageous in biomedical research because the new knowledge can be applied to both human health and livestock production, the latter of which, as we have discussed, is critical for agricultural sustainability and food security (Figure 1). Beyond the dual purpose with dual benefit paradigm, livestock species, particularly ruminants, have some advantages to biomedicine compared with rodent models. Specifically, ruminants are not litter-bearing, have longer gestation lengths and in the case of cattle, timing of organ development is similar to that of humans, *in vivo* measurements are more easily obtained, and an abundance of tissue and bodily fluids are available.

Importance of livestock in and of themselves

Livestock are of great importance in providing high-quality protein and micronutrients in the human diet. In fact, the availability of animal protein is linked to the rate of economic development in developing countries.[200,201] Furthermore, as the world's population continues to increase, so does the demand for animal protein because of its value as a nutrient-dense high-quality food.[202–204] Additionally, skeletal muscle mass and function, which is dependent on adequate protein consumption, are key components in human health and well-being.

Future directions and recommendations

Very early during gestation, nutrients are supplied to the fetus primarily through the histotroph (uterine secretions), and as the placenta develops, it becomes the primary organ for nutrient delivery to the developing offspring (Reynolds *et al.*, 2023a). Research utilizing livestock models to investigate the effects of nutritional supplementation during pregnancy on utero-placental nutrient delivery, specific nutrient demands for developing tissues, microbiome and epigenetic mechanisms responsible for developmental programming, cardiovascular and metabolic function in the fetus and offspring, and transgenerational impacts should improve our understanding of, and hence management and

https://doi.org/10.1017/S2040174426100452 Published online by Cambridge University Press

therapeutic strategies for fostering the positive and mitigating the negative aspects of, developmental programming.

Furthermore, we are convinced not only of the value of livestock models, as discussed already, but also of the value of epidemiological and transgenerational studies in humans and other species in furthering our understanding of the underlying mechanisms and consequences of developmental origins of health and disease.

Acknowledgments. None.

Financial support. This publication is a contribution of the South Dakota Agricultural Experiment Station. This material is based upon work that is supported in part by the National Institute of Food and Agriculture, U.S. Department of Agriculture, Hatch project under accession number 7,009,601 (R.M.S.).

Competing interests. The authors declare none. To the authors knowledge, all studies discussed in this invited review have followed ethical standards for animal and human research.

Ethical standard. This is a review paper. There is no human or animal research conducted in this paper. This paper has reviewed research papers, which each provide their own ethical standards statements.

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