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Postnatal nutrient repartitioning due to adaptive developmental programming.

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Introduction

The consequences of prenatal stress on lifelong metabolic function and health was first proposed by David Barker and Nicholas Hales with the publication of their Thrifty Phenotype Hypothesis in the early 1990s.^{1,2} Subsequent studies in humans and animals have further demonstrated that stress-induced adaptive fetal programming leads to tissue-specific changes in metabolic function and growth capacity.^{3,4} Developmental adaptations to the intrauterine nutrient restriction that accompanies most maternofetal stressors target regulatory pathways for nutrient utilization in non-essential tissues such as skeletal muscle.⁴⁻⁶ This aids intrauterine survival by re-appropriating nutrients to support neural, cardiac, and endocrine tissue function but reduces metabolic efficiency and growth capacity in offspring. Stress-induced fetal adaptations are typically characterized by intrauterine growth restriction (IUGR) during late gestation and low birthweight.^{7,8} Poor postnatal growth and metabolic inefficiency associated with low birthweight can reduce value in livestock.^{4,8} Experimental models of IUGR livestock show how maternofetal stress from environmental, nutritional, or health conditions lead to fetal metabolic adaptations,^{5,9,10} but few studies have followed IUGR-born livestock after birth. Even less is known about how adaptive changes alter nutrient utilization in these offspring. In this review, we summarize the current literature that assesses nutrient partitioning in IUGR-born animals. In addition, we describe the key adaptive mechanisms underlying developmental changes that reduced muscle growth and impair metabolism.

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The IUGR Phenotype

IUGR is a product of developmental adaptations.

Studies in IUGR fetal sheep and other animals show that asymmetric fetal growth restriction is a consequence of nutrient-sparing developmental adaptations.^{5,11} These adaptations most commonly result from placental insufficiency produced by sustained maternal stress during mid-gestation.^{11,12} Placental insufficiency can result from a number of environmental challenges including heat stress, nutrient restriction, illness, but produces consistent developmental outcomes in the fetus.^{12,13} Regardless of the maternal/placental insult, placental insufficiency induces changes in metabolic tissues such as skeletal muscle, pancreas, liver, and adipose tissues,¹⁴⁻¹⁶ as summarized in Table 1. Together, these collective adaptive responses alter systemic nutrient repartitioning by reducing substrate utilization by non-visceral soft tissues in favor of critical brain, heart, lungs, and endocrine tissues.^{13,17} Restriction of skeletal muscle growth, insulin sensitivity, and pancreatic function are chief among these fetal adaptations.^{3,11,14-16}

IUGR adaptations persist in offspring.

Thrifty metabolic adaptations that develop during gestation persist after birth despite alleviation of prenatal stressors.^{2,18} The first evidence that prenatal stress is associated with postnatal metabolic dysfunction arose from Barker's epidemiological studies of socioeconomic classes in the UK. In poorer industrial populations, high rates of low birthweight infants correlated with greater incidence of hypertension, obesity, type 2 diabetes, and glucose intolerance in adulthood.^{1,2} Low birthweight individuals also exhibit lifelong reductions in lean mass and increased fat deposition.¹⁹⁻²¹ These results have since been corroborated in other human populations.^{22,23} Moreover, low birthweight livestock exhibit similar changes in body composition and metabolic function,^{18,24,25} as illustrated in Figure 1. Recent research by our lab and others has focused on understanding the molecular mechanisms that link developmental adaptations *in utero* with lifelong changes in metabolic function, nutrient utilization, and growth capacity.

Postnatal Growth Characteristics in IUGR-born Livestock

Low birthweight animals exhibit altered body composition.

Similar to low birthweight children,²⁶ low birthweight animals demonstrate accelerated neonatal "catch up" growth that is driven by increased fat deposition rather than muscle growth.^{18,27} In fact, persistence of poor muscle growth leads to a reduction in carcass yield, smaller high-value cuts from the loin and upper hindlimb, and increased fat thickness in both cattle and sheep.^{18,28} Reduced muscle growth and increased adiposity appear to occur via independent mechanisms, and it is worth noting that fat deposits are actually reduced in the IUGR fetus due to greater mobilization.²⁹ Greater adiposity in offspring appears to be secondary to impaired muscle growth, as a smaller proportion of dietary nutrients are utilized for muscle growth and thus more are stored as fat.^{18,30} Conversely, studies by our lab and others show that impaired skeletal muscle growth is the product of intrinsic myoblast dysfunction.^{12,14,31,32}

Skeletal muscle growth is disproportionally reduced.

Reduced lean mass and muscle size in low birthweight livestock at harvest^{28,33-36} is the result of impaired hypertrophic muscle growth. In IUGR fetal sheep, we observed reduced cross-sectional areas of hindlimb muscle fibers by as much as 50% but no reduction in fiber numbers.^{14,31} Muscle fibers remained smaller in IUGR-born lambs at one month of age, or ~20kg BW.^{28,37} Myoblast function is the rate-limiting step in hypertrophic muscle growth,³⁸ and impaired skeletal muscle growth in IUGR fetal and neonatal sheep coincided with intrinsic deficits in myoblast proliferative and differentiation capacities.^{31,32,37,39} Skeletal muscle is the greatest utilizer of glucose in the body,^{40,41} and utilization per gram of muscle is not reduced in the IUGR fetus or lamb^{10,11,42}. Thus, restricting skeletal muscle mass is a key mechanism for repartitioning the limited glucose supply in the IUGR fetus from muscle to vital tissue function and development. However, persistent deficits in muscle growth capacity in IUGR-born livestock reduce their value in meat production.⁴

Skeletal muscle protein accretion is reduced.

Similar to glucose, skeletal muscle in low birthweight livestock utilize less protein during early growth.²⁸ Recent studies by Laura Brown's laboratory help point out several key mechanisms for adaptive changes in muscle protein utilization. As IUGR fetuses approach term, their rates of skeletal muscle protein breakdown remain comparable to uncompromised fetuses.⁴³ However, protein synthesis and accretion rates in IUGR skeletal muscle drop by as much as 50%, which is similar to reduction in amino acid uptake and utilization.⁴³ Moreover, the effects of IUGR on circulating amino acid concentrations vary widely among individual amino acids.^{43,44} For example, tyrosine, arginine, and isoleucine concentrations were reduced in IUGR fetal blood; however, taurine, glycine, and alanine concentrations were increased.⁴³ Increasing amino acid supply via direct fetal infusion did not increase protein accretion or synthesis rates, muscle size, or fetal mass but increased amino acid oxidation rates.⁴⁴ Thus, reduced protein uptake and accretion by IUGR skeletal muscle does not appear to be the direct result of reduced fetal protein availability. Rather, it may be a product of β adrenergic adaptations due to chronic hypercatecholaminemia, as hypercatecholaminemia was not mitigated by amino acid infusion in this study. β 2 adrenergic stimulation increases protein synthesis and cycling⁴⁵ but gene expression for the β 2 adrenergic receptor is reduced in IUGR skeletal muscle.⁴ When hypercatecholaminemia was mitigated by adrenal demedullation in IUGR fetal sheep, fetal mass was increased by 50-60%.^{46,47} Diminished blood flow, reduced oxygen utilization, and hypoinsulinemia may also contribute to reduced protein accretion in IUGR muscle.^{43,48}

Tissue-Specific Metabolic Changes in IUGR Livestock

Skeletal muscle glucose metabolism is altered.

In humans, skeletal muscle from IUGR-born individuals show evidence of impaired insulin responsiveness and reduced glucose oxidative metabolism.^{22,23,49-51} Studies in IUGR fetal sheep show that reduced whole-body glucose oxidation rates are present near term and occur despite normal rates of glucose uptake and utilization.^{10,11} We showed that reduced glucose oxidation is muscle-specific in the IUGR fetal sheep and neonatal lamb.^{4,52,53} In concert with reduced glucose oxidation, IUGR skeletal muscle increases lactate production,^{9,10,41}

which unlike glucose can be secreted from skeletal muscle. Lactate can then be utilized by the liver for glucose production or by cardiac tissue for energy.^{11,54,55} The shift in IUGR skeletal muscle glucose metabolism coincides with a reduction in the proportion of oxidative muscle fibers relative to glycolytic fibers.¹⁴ We are not aware of any studies measuring muscle fiber types in low birthweight offspring of ruminant livestock, but reductions in oxidative-to-glycolytic muscle fiber types have been observed in IUGR-born humans⁵⁶ and mice.⁵⁷

Like reduced muscle growth, the metabolic shift in IUGR skeletal muscle appears to be at least partially due to changes in adrenergic activity. Studies by our lab and others have shown that skeletal muscle insulin action and glucose oxidation are stimulated by β_2 adrenergic activity but reduced by β_1 activity.⁵⁸⁻⁶⁰ Fetal hypoxemia increases circulating catecholamine levels,⁶¹ and chronic adrenergic exposure during late gestation reduces β_2 -to- β_1 adrenergic receptor gene expression in IUGR skeletal muscle.⁴ It is worth noting that slow oxidative muscle fibers express more β adrenergic receptors than fast glycolytic fibers^{62,63} and thus may be affected by chronic hypercatecholaminemia to a greater extent.

Fat deposition is increased.

Adaptive changes in IUGR skeletal muscle nutrient utilization cause a greater proportion of dietary nutrients to be deposited into central fat stores.^{18,26,35} In addition, IUGR fetal adipocytes undergo developmental adaptations increase their ability to proliferate and expand in size, which increases their ability to store more fat.⁶⁴ IUGR-born male rats indicate a possible adaptive mechanism is the increased activity of peroxisome proliferator-activated receptor gamma (PPAR γ), which is a primary regulator of adipogenesis and lipogenesis.¹⁶ Other studies have implicated greater expression of the lipogenic proteins, acetyl-CoA carboxylase- α , fatty acid synthase, and ATP-binding cassette transporter 1.^{65,66}

Adipose tissue plays an indirect role in systemic metabolic regulation related to its effects on endocrine and immune function, and greater fat mass in IUGR-born animals disrupts these functions.⁶⁷ Immunomodulatory disruptions in IUGR-born ruminants precede obesity and are attributable to increased infiltration of macrophages into visceral and subcutaneous fat depots, creating tissue inflammation that further contributes to insulin resistance, metabolic dysfunction, and poor growth.^{67,68} Hyperlipidemia also increases systemic inflammation in humans,⁶⁹ although we are not aware of any similar studies in ruminant livestock. This occurs via activation of toll-like receptor 4 (TLR4) by free fatty acids, which in turn upregulates inflammatory pathways that impair insulin signaling and induce metabolic dysfunction.⁶⁹

Changes in hepatic function contribute to metabolic dysfunction.

Lipid homeostasis is regulated in large part by liver function, and adaptations in hepatic development contribute to metabolic dysfunction in IUGR offspring.⁷⁰⁻⁷² In sheep, IUGR liver mass is reduced in the near term fetus and in offspring.^{71,73} Hepatic expression of gluconeogenic enzymes including PEPCK and G6P are increased in response to chronic hypoglycemia near term.^{11,71} However, the impact on postnatal gluconeogenesis is less clear, as gluconeogenic enzymes remained elevated into adulthood in IUGR-born rats^{74,75}

but are normal or even reduced in IUGR-born lambs.^{76,77} Conversely, hepatic glycogen content is normal in IUGR fetal sheep^{11,71} but reduced at 1 month of age.⁷³

Hepatic adaptations in the IUGR fetus diminish activation of nutrient-sensing proteins including AMPK, mTOR, SIRT1.⁷¹ This adaptation likely spares fetal hepatocytes from apoptosis but also contributes to hepatic inflammation, dyslipidemia, and reduced insulin responsiveness in offspring.^{70,71,78} These pathologies are likely mediated at least in part by persistent reductions in the expression of PPAR α and PPAR γ .⁷⁰ Reduced lipogenesis in concert with dyslipidemia and reduced fatty acid oxidation enhance inflammatory responses in the liver and increase the synthesis of triglycerides,⁷⁰ further contributing to systemic insulin desensitization.

β -cell dysfunction impairs insulin secretion.

Insulin secretion from pancreatic β -cells is the primary regulator of glucose uptake and metabolism and contributes to anabolic processes and muscle growth.^{15,79} β -cell dysfunction is a chief factor in increased risk for metabolic dysfunction IUGR offspring.¹⁵ In low birthweight lambs, insulin stimulus-secretion coupling is enhanced at one week⁴² and two months of age⁸¹ due to residual compensation in sensitivity to glucose that develops *in utero*.⁸¹⁻⁸³ Compensatory increases are transient, however, and adaptive impairment of glucose-stimulated insulin secretion is apparent by 8 months of age,⁸¹ as illustrated in Figure 2. The severity of β -cell dysfunction is typically proportional to the severity of placental insufficiency and is at least in part associated with impaired islet development.^{15,84} IUGR fetal sheep exhibit reduced β -cell mass and intracellular insulin concentrations near term, despite minimal effects on other endocrine cell types within the islets.^{15,84,85} This appears to be the product of changes in adrenergic regulation due to chronic fetal hypercatecholaminemia, which altered catecholamine-responsive genes associated with both cellular development and function.⁸⁰ In addition, islets isolated from these fetuses had impaired glucose oxidation capacity,^{84,85} which is a key step in secretion-stimulus coupling. Developmental adaptations in IUGR fetal islets appear to be the result of chronic adrenergic exposure, as 7-day norepinephrine infusion into otherwise uncompromised fetal sheep produced similar effects.^{86,87}

Summary

Stress-induced adaptive fetal programming leads to intrauterine growth restriction and low birthweight. Low birthweight livestock are characterized by changes in nutrient partitioning, tissue-specific metabolic function, growth, and body composition. Studies in cattle and sheep show that these adaptations result in poor growth efficiency and carcass value. Skeletal muscle nutrient utilization appears to be disproportionately targeted by fetal adaptations to stress, as glucose oxidation and protein accretion are impaired. These changes coincide with reductions in slow oxidative fiber proportions, insulin responsiveness, hypertrophic growth, and β 2 adrenergic stimulation. In low birthweight offspring, adaptations reduce nutrient utilization for muscle growth. Instead, a greater amount of dietary nutrients are stored as visceral fat. Adaptive changes in functional development of adipocytes, liver tissues, and pancreatic β -cells further contribute to metabolic inefficiency

and body composition changes. Poor muscle growth together with greater fat deposition leads to less efficient feed conversion, lower yields, smaller high-value cuts, and reduced value in low birthweight livestock.

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References

- Hales C, Barker D, Clark P, Cox L, Fall C, Osmond C, Winter P. Fetal and infant growth and impaired glucose tolerance at age 64. *Bmj*. 1991;303(6809):1019–1022. [PubMed: 1954451]
- Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. *Diabetologia*. 1992;35(7):595–601. [PubMed: 1644236]
- Funston RN, Summers AF. Effect of prenatal programming on heifer development. *Vet Clin North Am Food Anim Pract*. 2013;29(3):517–536. [PubMed: 24182432]
- Yates DT, Petersen JL, Schmidt TB, Cadaret CN, Barnes TL, Posont RJ, Beede KA. ASAS-SSR Triennial Reproduction Symposium: Looking Back and Moving Forward- How Reproductive Physiology has Evolved: Fetal origins of impaired muscle growth and metabolic dysfunction: Lessons from the heat-stressed pregnant ewe. *J Anim Sci*. 2018;96(7):2987–3002. [PubMed: 29701769]
- Yates DT, Macko AR, Nearing M, Chen X, Rhoads RP, Limesand SW. Developmental programming in response to intrauterine growth restriction impairs myoblast function and skeletal muscle metabolism. *J Pregnancy*. 2012;2012:631038. [PubMed: 22900186]
- Yates DT, Green AS, Limesand SW. Catecholamines mediate multiple fetal adaptations during placental insufficiency that contribute to intrauterine growth restriction: lessons from hyperthermic sheep. *J Pregnancy*. 2011;2011(Article ID 740408):740408. [PubMed: 21773031]
- Galan HL, Hussey MJ, Barbera A, Ferrazzi E, Chung M, Hobbins JC, Battaglia FC. Relationship of fetal growth to duration of heat stress in an ovine model of placental insufficiency. *Am J Obstet Gynecol*. 1999;180(5):1278–1282. [PubMed: 10329890]
- Limesand SW, Rozance PJ. Fetal adaptations in insulin secretion result from high catecholamines during placental insufficiency. *J Physiol*. 2017;595(15):5103–5113. [PubMed: 28194805]
- Thorn SR, Rozance PJ, Brown LD, Hay WW. The Intrauterine Growth Restriction Phenotype: Fetal Adaptations and Potential Implications for Later Life Insulin Resistance and Diabetes. *Semin Reprod Med*. 2011;29(03):225,236. [PubMed: 21710398]
- Brown LD, Rozance PJ, Bruce JL, Friedman JE, Hay WW Jr., Wesolowski SR. Limited capacity for glucose oxidation in fetal sheep with intrauterine growth restriction. *Am J Physiol Regul Integr Comp Physiol*. 2015;309(8):R920–928. [PubMed: 26224688]
- Limesand SW, Rozance PJ, Smith D, Hay WW Jr. Increased insulin sensitivity and maintenance of glucose utilization rates in fetal sheep with placental insufficiency and intrauterine growth restriction. *Am J Physiol Endocrinol Metab*. 2007;293(6):E1716–1725. [PubMed: 17895285]
- Soto SM, Blake AC, Wesolowski SR, Rozance PJ, Barthel KB, Gao B, Hetrick B, McCurdy CE, Garza NG, Hay WW Jr., Leinwand LA, Friedman JE, Brown LD. Myoblast replication is reduced in the IUGR fetus despite maintained proliferative capacity in vitro. *J Endocrinol*. 2017;232(3):475–491. [PubMed: 28053000]
- Morrison JL. Sheep models of intrauterine growth restriction: fetal adaptations and consequences. *Clin Exp Pharmacol Physiol*. 2008;35(7):730–743. [PubMed: 18498533]
- Yates DT, Cadaret CN, Beede KA, Riley HE, Macko AR, Anderson MJ, Camacho LE, Limesand SW. Intrauterine growth-restricted sheep fetuses exhibit smaller hindlimb muscle fibers and lower

proportions of insulin-sensitive Type I fibers near term. *Am J Physiol Regul Integr Comp Physiol*. 2016;310(11):R1020–1029. [PubMed: 27053651]

15. Boehmer BH, Limesand SW, Rozance PJ. The impact of IUGR on pancreatic islet development and beta-cell function. *J Endocrinol*. 2017;235(2):R63–76. [PubMed: 28808079]
16. Joss-Moore LA, Wang Y, Campbell MS, Moore B, Yu X, Callaway CW, McKnight RA, Desai M, Moyer-Mileur LJ, Lane RH. Uteroplacental insufficiency increases visceral adiposity and visceral adipose PPARgamma2 expression in male rat offspring prior to the onset of obesity. *Early Hum Dev*. 2010;86(3):179–185. [PubMed: 20227202]
17. Rosenberg A. The IUGR newborn; Paper presented at: Seminars in perinatology; 2008.
18. De Blasio MJ, Gatford KL, Robinson JS, Owens JA. Placental restriction of fetal growth reduces size at birth and alters postnatal growth, feeding activity, and adiposity in the young lamb. *Am J Physiol Regul Integr Comp Physiol*. 2007;292(2):R875–886. [PubMed: 17023666]
19. Hediger ML, Overpeck MD, Kuczmarski RJ, McGlynn A, Maurer KR, Davis WW. Muscularity and fatness of infants and young children born small- or large-for-gestational-age. *Pediatrics*. 1998;102(5):E60. [PubMed: 9794990]
20. Kensara OA, Wootton SA, Phillips DI, Patel M, Jackson AA, Elia M, Grp HS. Fetal programming of body composition: relation between birth weight and body composition measured with dual-energy X-ray absorptiometry and anthropometric methods in older Englishmen. *Am J Clin Nutr*. 2005;82(5):980–987. [PubMed: 16280428]
21. Yliharsila H, Kajantie E, Osmond C, Forsen T, Barker DJP, Eriksson JG. Birth size, adult body composition and muscle strength in later life. *Int J Obes*. 2007;31(9):1392–1399.
22. Flanagan DE, Moore VM, Godsland IF, Cockington RA, Robinson JS, Phillips DI. Fetal growth and the physiological control of glucose tolerance in adults: a minimal model analysis. *Am J Physiol Endocrinol Metab*. 2000;278(4):E700–706. [PubMed: 10751205]
23. Ong KK, Ahmed ML, Emmett PM, Preece MA, Dunger DB. Association between postnatal catch-up growth and obesity in childhood: prospective cohort study. *BMJ*. 2000;320(7240):967–971. [PubMed: 10753147]
24. Gondret F, Lefaucheur L, Louveau I, Lebreton B, Pichodo X, Le Cozler Y. Influence of piglet birth weight on postnatal growth performance, tissue lipogenic capacity and muscle histological traits at market weight. *Livestock Production Science*. 2005;93(2):137–146.
25. De Blasio MJ, Gatford KL, McMillen IC, Robinson JS, Owens JA. Placental restriction of fetal growth increases insulin action, growth, and adiposity in the young lamb. *Endocrinology*. 2007;148(3):1350–1358. [PubMed: 17110432]
26. Zarrati M, Shidfar F, Razmpoosh E, Nezhad FN, Keivani H, Hemami MR, Asemi Z. Does low birth weight predict hypertension and obesity in schoolchildren? *Ann Nutr Metab*. 2013;63(1-2):69–76. [PubMed: 23942014]
27. Madsen JG, Bee G. Compensatory growth feeding strategy does not overcome negative effects on growth and carcass composition of low birth weight pigs. *Anim*. 2015;9(3):427–436.
28. Greenwood PL, Hunt AS, Hermanson JW, Bell AW. Effects of birth weight and postnatal nutrition on neonatal sheep: II. Skeletal muscle growth and development. *J Anim Sci*. 2000;78(1):50–61. [PubMed: 10682802]
29. Gondret F, Pèrè M-C, Tacher S, Daré S, Trefeu C, Le Huërou-Luron I, Louveau I. Spontaneous intra-uterine growth restriction modulates the endocrine status and the developmental expression of genes in porcine fetal and neonatal adipose tissue. *General and comparative endocrinology*. 2013;194:208–216. [PubMed: 24095810]
30. Liu H, Schultz CG, De Blasio MJ, Peura AM, Heinemann GK, Harryanto H, Hunter DS, Wooldridge AL, Kind KL, Giles LC, Simmons RA, Owens JA, Gatford KL. Effect of placental restriction and neonatal exendin-4 treatment on postnatal growth, adult body composition, and in vivo glucose metabolism in the sheep. *Am J Physiol Endocrinol Metab*. 2015;309(6):E589–600. [PubMed: 26219868]
31. Yates DT, Clarke DS, Macko AR, Anderson MJ, Shelton LA, Nearing M, Allen RE, Rhoads RP, Limesand SW. Myoblasts from intrauterine growth-restricted sheep fetuses exhibit intrinsic deficiencies in proliferation that contribute to smaller semitendinosus myofibers. *J Physiol*. 2014;592(Pt 14):3113–3125. [PubMed: 24860171]

32. Posont R, Beede K, Limesand S, Yates D. Changes in myoblast responsiveness to TNF α and IL-6 contribute to decreased skeletal muscle mass in intrauterine growth restricted fetal sheep. . *Translational Animal Science*. 2018;2(Suppl1):S44–S47. [PubMed: 30627704]
33. Hegarty PV, Allen CE. Effect of pre-natal runting on the post-natal development of skeletal muscles in swine and rats. *J Anim Sci*. 1978;46(6):1634–1640. [PubMed: 690014]
34. Powell SE, Aberle ED. Skeletal muscle and adipose tissue cellularity in runt and normal birth weight swine. *J Anim Sci*. 1981;52(4):748–756. [PubMed: 7196399]
35. Greenwood PL, Cafe LM. Prenatal and pre-weaning growth and nutrition of cattle: longterm consequences for beef production. *Anim*. 2007;1(9):1283–1296.
36. Greenwood PL, Hunt AS, Hermanson JW, Bell AW. Effects of birth weight and postnatal nutrition on neonatal sheep: I. Body growth and composition, and some aspects of energetic efficiency. *J Anim Sci*. 1998;76(9):2354–2367. [PubMed: 9781492]
37. Camacho LE, Yates DT, Davenport HM, Allen RE, Limesand SW. Decreased Satellite Cell Proliferation Rates Contribute to Small Fibers in the Semitendinosus Muscle of Intrauterine Growth Restricted Lambs. *Reprod Sci*. 2016;23(Supplement 1):316A.
38. Allen DL, Roy RR, Edgerton VR. Myonuclear domains in muscle adaptation and disease. *Muscle Nerve*. 1999;22(10):1350–1360. [PubMed: 10487900]
39. Greenwood PL, Slepatis RM, Bell AW, Hermanson JW. Intrauterine growth retardation is associated with reduced cell cycle activity, but not myofibre number, in ovine fetal muscle. *Reprod Fert Dev*. 1999;11(5):281–291.
40. DeFronzo RA, Jacot E, Jequier E, Maeder E, Wahren J, Felber JP. The effect of insulin on the disposal of intravenous glucose. Results from indirect calorimetry and hepatic and femoral venous catheterization. *Diabetes*. 1981;30(12):1000–1007. [PubMed: 7030826]
41. Brown LD. Endocrine regulation of fetal skeletal muscle growth: impact on future metabolic health. *J Endocrinol*. 2014;221(2):R13–29. [PubMed: 24532817]
42. Camacho LE, Chen X, Hay WW Jr., Limesand SW. Enhanced insulin secretion and insulin sensitivity in young lambs with placental insufficiency-induced intrauterine growth restriction. *Am J Physiol Regul Integr Comp Physiol*. 2017;313(2):R101–R109. [PubMed: 28490449]
43. Rozance PJ, Zastoupil L, Wesolowski SR, et al. Skeletal muscle protein accretion rates and hindlimb growth are reduced in late gestation intrauterine growthrestricted fetal sheep. *J Physiol*. 2018;596(1):67–82. [PubMed: 28940557]
44. Wai SG, Rozance PJ, Wesolowski SR, Hay WW Jr., Brown LD. Prolonged amino acid infusion into intrauterine growth restricted fetal sheep increases leucine oxidation rates. *Am J Physiol Endocrinol Metab*. 2018.
45. Hostrup M, Reitelsheder S, Jessen S, Kalsen A, Nyberg M, Egelund J, Kreiberg M, Kristensen CM, Thomassen M, Pilegaard H, Backer V, Jacobson GA, Holm L, Bangsbo J. Beta2-adrenoceptor agonist salbutamol increases protein turnover rates and alters signalling in skeletal muscle after resistance exercise in young men. *The Journal of Physiology*. 2018;596(17):4121–4139. [PubMed: 29968301]
46. Macko AR, Yates DT, Chen X, Shelton LA, Kelly AC, Davis MA, Camacho LE, Anderson MJ, Limesand SW. Adrenal Demedullation and Oxygen Supplementation Independently Increase Glucose-Stimulated Insulin Concentrations in Fetal Sheep With Intrauterine Growth Restriction. *Endocrinol*. 2016;157(5):2104–2115.
47. Davis MA, Macko AR, Steyn LV, Anderson MJ, Limesand SW. Fetal adrenal demedullation lowers circulating norepinephrine and attenuates growth restriction but not reduction of endocrine cell mass in an ovine model of intrauterine growth restriction. *Nutrients*. 2015;7(1):500–516. [PubMed: 25584967]
48. Limesand SW, Rozance PJ, Brown LD, Hay WW Jr. Effects of chronic hypoglycemia and euglycemic correction on lysine metabolism in fetal sheep. *Am J Physiol Endocrinol Metab*. 2009;296(4):E879–887. [PubMed: 19190258]
49. Mericq V, Ong KK, Bazaes R, Pena V, Avila A, Salazar T, Soto N, Iniguez G, Dunger DB. Longitudinal changes in insulin sensitivity and secretion from birth to age three years in small- and appropriate-for-gestational-age children. *Diabetologia*. 2005;48(12):2609–2614. [PubMed: 16283238]

50. Jornayvaz FR, Selz R, Tappy L, Theintz GE. Metabolism of oral glucose in children born small for gestational age: evidence for an impaired whole body glucose oxidation. *Metabolism*. 2004;53(7): 847–851. [PubMed: 15254875]
51. Ozanne S, Jensen C, Tingey K, Storgaard H, Madsbad S, Vaag A. Low birthweight is associated with specific changes in muscle insulin-signalling protein expression. *Diabetologia*. 2005;48(3): 547–552. [PubMed: 15729577]
52. Cadaret C, Merrick E, Barnes T, Beede K, Posont R, Petersen J, Yates D. Sustained maternal inflammation during the early third trimester yields fetal adaptations that impair subsequent skeletal muscle growth and glucose metabolism in sheep. *Translational Animal Science*. 2018;2(Suppl1):S14–S18. [PubMed: 30627702]
53. Merrick EM, Cadaret CN, Barnes TL, Beede KA, Yates DT. Metabolic regulation by stress systems in bovine myoblasts and ovine fetal skeletal muscle. *Proc West Sect Am Soc Anim Sci*. 2017;68:87–91.
54. Barry JS, Davidsen ML, Limesand SW, Galan HL, Friedman JE, Regnault TR, Hay WW Jr. Developmental changes in ovine myocardial glucose transporters and insulin signaling following hyperthermia-induced intrauterine fetal growth restriction. *Exp Biol Med (Maywood)*. 2006;231(5):566–575. [PubMed: 16636305]
55. Thorn SR, Brown LD, Rozance PJ, Hay WW Jr., Friedman JE. Increased hepatic glucose production in fetal sheep with intrauterine growth restriction is not suppressed by insulin. *Diabetes*. 2013;62(1):65–73. [PubMed: 22933111]
56. Jensen CB, Storgaard H, Madsbad S, et al. Altered skeletal muscle fiber composition and size precede whole-body insulin resistance in young men with low birth weight. *J Clin Endocrinol Metab* 2007;92(4):1530–4. [PubMed: 17284623]
57. Beauchamp B, Ghosh S, Dysart MW, Kanaan GN, Chu A, Blais A, Rajamanickam K, Tsai EC, Patti ME, Harper ME. Low birth weight is associated with adiposity, impaired skeletal muscle energetics and weight loss resistance in mice. *Int J Obes (Lond)*. 2015;39(4):702–711. [PubMed: 25091727]
58. Cadaret CN, Beede KA, Riley HE, Yates DT. Acute exposure of primary rat soleus muscle to zilpaterol HCl (beta2 adrenergic agonist), TNFalpha, or IL-6 in culture increases glucose oxidation rates independent of the impact on insulin signaling or glucose uptake. *Cytokine*. 2017;96:107–113. [PubMed: 28390265]
59. Barnes T, Kubik R, Cadaret C, Beede K, Merrick E, Chung S, Schmidt T, Petersen J, Yates D. Identifying hyperthermia in heat-stressed lambs and its effects on β agonist-stimulated glucose oxidation in muscle. *Proc West Sect Am Soc Anim Sci*. 2017;68:106–110.
60. Hoeks J, van Baak MA, Hesselink MKC, Hul GB, Vidal H, Saris WHM, Schrauwen P. Effect of β 1- and β 2-adrenergic stimulation on energy expenditure, substrate oxidation, and UCP3 expression in humans. *Am J Physiol Endocrinol Metab*. 2003;285(4):E775–E782. [PubMed: 12824081]
61. Yates DT, Macko AR, Chen X, Green AS, Kelly AC, Anderson MJ, Fowden AL, Limesand SW. Hypoxaemia-induced catecholamine secretion from adrenal chromaffin cells inhibits glucose-stimulated hyperinsulinaemia in fetal sheep. *The Journal of Physiology*. 2012;590(21):5439–5447. [PubMed: 22907052]
62. Williams RS, Caron MG, Daniel K. Skeletal muscle beta-adrenergic receptors: variations due to fiber type and training. *Am J Physiol*. 1984;246(2 Pt 1):E160–167. [PubMed: 6320672]
63. Martin W, Murphree S, Saffitz J. Beta-adrenergic receptor distribution among muscle fiber types and resistance arterioles of white, red, and intermediate skeletal muscle. *Circulation Research*. 1989;64(6):1096–1105. [PubMed: 2541942]
64. Desai M, Ross MG. Fetal programming of adipose tissue: effects of intrauterine growth restriction and maternal obesity/high-fat diet. *Semin Reprod Med*. 2011;29(3):237–245. [PubMed: 21710399]
65. Yee JK, Han G, Vega J, Lee WP, Ross MG, Desai M. Fatty Acid de Novo Synthesis in Adult Intrauterine Growth-Restricted Offspring, and Adult Male Response to a High Fat Diet. *Lipids*. 2016;51(12):1339–1351. [PubMed: 27660207]

66. Zinkhan EK, Yu B, Callaway CW, McKnight RA. Intrauterine growth restriction combined with a maternal high-fat diet increased adiposity and serum corticosterone levels in adult rat offspring. *J Dev Orig Health Dis.* 2018;9(3):315–328. [PubMed: 29397052]
67. Ampem G, Azegrouz H, Bacsadi A, Balogh L, Schmidt S, Thuroczy J, Roszer T. Adipose tissue macrophages in non-rodent mammals: a comparative study. *Cell Tissue Res.* 2016;363(2):461–478. [PubMed: 26239911]
68. Veiga-Lopez A, Moeller J, Sreedharan R, Singer K, Lumeng C, Ye W, Pease A, Padmanabhan V. Developmental programming: interaction between prenatal BPA exposure and postnatal adiposity on metabolic variables in female sheep. *Am J Physiol Endocrinol Metab.* 2016;310(3):E238–247. [PubMed: 26646100]
69. Reyna SM, Ghosh S, Tantiwong P, Meka CS, Eagan P, Jenkinson CP, Cersosimo E, Defronzo RA, Coletta DK, Sriwijitkamol A, Musi N. Elevated toll-like receptor 4 expression and signaling in muscle from insulin-resistant subjects. *Diabetes.* 2008;57(10):2595–2602. [PubMed: 18633101]
70. Alisi A, Panera N, Agostoni C, Nobili V. Intrauterine growth retardation and nonalcoholic Fatty liver disease in children. *Int J Endocrinol.* 2011;2011:269853. [PubMed: 22190925]
71. Thorn SR, Regnault TR, Brown LD, Rozance PJ, Keng J, Roper M, Wilkening RB, Hay WW Jr., Friedman JE. Intrauterine growth restriction increases fetal hepatic gluconeogenic capacity and reduces messenger ribonucleic acid translation initiation and nutrient sensing in fetal liver and skeletal muscle. *Endocrinol.* 2009;150(7):3021–3030.
72. Roberts A, Nava S, Bocconi L, Salmona S, Nicolini U. Liver function tests and glucose and lipid metabolism in growth-restricted fetuses. *Obstet Gynecol.* 1999;94(2):290–294. [PubMed: 10432145]
73. Hyatt MA, Butt EA, Budge H, Stephenson T, Symonds ME. Effects of maternal cold exposure and nutrient restriction on the ghrelin receptor, the GH-IGF axis, and metabolic regulation in the postnatal ovine liver. *Reproduction.* 2008;135(5):723–732. [PubMed: 18304988]
74. Luo K, Chen P, Xie Z, Li W, Li S, He M. Effect of intrauterine growth retardation on gluconeogenic enzymes in rat liver. *Zhong Nan Da Xue Xue Bao Yi Xue Ban.* 2014;39(4):395–400. [PubMed: 24820282]
75. Lane RH, MacLennan NK, Hsu JL, Janke SM, Pham TD. Increased hepatic peroxisome proliferator-activated receptor-gamma coactivator-1 gene expression in a rat model of intrauterine growth retardation and subsequent insulin resistance. *Endocrinol.* 2002;143(7):2486–2490.
76. Rattanatray L, Muhlhausler BS, Nicholas LM, Morrison JL, McMillen IC. Impact of maternal overnutrition on gluconeogenic factors and methylation of the phosphoenolpyruvate carboxykinase promoter in the fetal and postnatal liver. *Pediatr Res.* 2014;75(1-1):14–21. [PubMed: 24452591]
77. Nicholas LM, Rattanatray L, MacLaughlin SM, Ozanne SE, Kleemann DO, Walker SK, Morrison JL, Zhang S, Muhlhausler BS, Martin-Gronert MS, McMillen IC. Differential effects of maternal obesity and weight loss in the periconceptional period on the epigenetic regulation of hepatic insulin-signaling pathways in the offspring. *Faseb j.* 2013;27(9):3786–3796. [PubMed: 23729590]
78. Magee TR, Han G, Cherian B, Khorram O, Ross MG, Desai M. Down-regulation of transcription factor peroxisome proliferator-activated receptor in programmed hepatic lipid dysregulation and inflammation in intrauterine growth-restricted offspring. *Am J Obstet Gynecol.* 2008;199(3):271.e271–275. [PubMed: 18667178]
79. Fu Z, Gilbert ER, Liu D. Regulation of insulin synthesis and secretion and pancreatic Beta-cell dysfunction in diabetes. *Curr Diabetes Rev.* 2013;9(1):25–53. [PubMed: 22974359]
80. Kelly AC, Bidwell CA, Chen X, Macko AR, Anderson MJ, Limesand SW. Chronic Adrenergic Signaling Causes Abnormal RNA Expression of Proliferative Genes in Fetal Sheep Islets. *Endocrinol.* 2018;159(10):3565–3578.
81. Ford SP, Hess BW, Schwoppe MM, Nijland MJ, Gilbert JS, Vonnahme KA, Means WJ, Han H, Nathanielsz PW. Maternal undernutrition during early to mid-gestation in the ewe results in altered growth, adiposity, and glucose tolerance in male offspring. *J Anim Sci.* 2007;85(5):1285–1294. [PubMed: 17224460]
82. Macko AR, Yates DT, Chen X, Green AS, Kelly AC, Brown LD, Limesand SW. Elevated plasma norepinephrine inhibits insulin secretion, but adrenergic blockade reveals enhanced β -cell

- responsiveness in an ovine model of placental insufficiency at 0.7 of gestation. *J Dev Orig Health Disease*. 2013;4(05):402–410. [PubMed: 24358443]
83. Leos RA, Anderson MJ, Chen X, Pugmire J, Anderson KA, Limesand SW. Chronic exposure to elevated norepinephrine suppresses insulin secretion in fetal sheep with placental insufficiency and intrauterine growth restriction. *Am J Physiol Endocrinol Metab*. 2010;298(4):E770–778. [PubMed: 20086198]
84. Limesand SW, Rozance PJ, Macko AR, Anderson MJ, Kelly AC, Hay WW Jr. Reductions in insulin concentrations and beta-cell mass precede growth restriction in sheep fetuses with placental insufficiency. *Am J Physiol Endocrinol Metab*. 2013;304(5):E516–523. [PubMed: 23277186]
85. Limesand SW, Rozance PJ, Zerbe GO, Hutton JC, Hay WW Jr. Attenuated insulin release and storage in fetal sheep pancreatic islets with intrauterine growth restriction. *Endocrinol*. 2006;147(3):1488–1497.
86. Chen X, Green AS, Macko AR, Yates DT, Kelly AC, Limesand SW. Enhanced insulin secretion responsiveness and islet adrenergic desensitization after chronic norepinephrine suppression is discontinued in fetal sheep. *Am J Physiol Endocrinol Metab*. 2014;306(1):E58–64. [PubMed: 24253046]
87. Chen X, Kelly AC, Yates DT, Macko AR, Lynch RM, Limesand SW. Islet adaptations in fetal sheep persist following chronic exposure to high norepinephrine. *J Endocrinol*. 2017;232(2):285–295. [PubMed: 27888197]

Key Points

- Fetal adaptations to nutritional stress lead to intrauterine growth restriction (IUGR) and low birthweight. This occurs in all mammalian species and is a long-standing challenge to food animal production.
- IUGR fetal adaptations repartition limited nutrients to vital neural, cardiac, and endocrine tissues by restricting skeletal muscle mass and nutrient utilization.
- Nutrient-sparing adaptations aid fetal survival of IUGR conditions but become problematic after birth when nutrient supply is not limited. IUGR-born offspring have less lean muscle and increased fat deposition, which reduces feed efficiency, carcass quality, and value.
- Developmental adaptations affect fat, liver, and pancreatic β -cells in addition to skeletal muscle. Changes include reduced tissue responsiveness to insulin, greater local inflammation, and altered β adrenergic tone.

Synopsis:

Fetal stress induces developmental adaptations that result in intrauterine growth restriction (IUGR) and low birthweight. These adaptations re-appropriate nutrients to the most essential tissues, which benefits fetal survival. The same adaptations are detrimental to growth efficiency and carcass value in livestock, however, as muscle is disproportionately targeted. IUGR adipocytes, liver tissues, and pancreatic β -cells also exhibit functional adaptations. Identifying mechanisms underlying adaptive changes is fundamental to improving outcomes and value in low birthweight livestock. In this review, we outline studies that have begun to identify stress-induced fetal adaptations affecting growth, metabolism, and differential nutrient utilization in IUGR-born animals.

Nutrient Partitioning in Low Birthweight Livestock

Figure 1.

Stress-induced fetal adaptations cause low birthweight livestock to re-appropriate dietary nutrients. Less nutrients are utilized for skeletal muscle growth and more are redirected to visceral fat deposits and, to a lesser extent, intramuscular and subcutaneous fat deposits.

Figure 2.

Stress induced fetal adaptations impair tissue responsiveness to insulin. In prenatal and early postnatal stages, impaired insulin action is masked by transient increases in insulin sensitivity, which benefits IUGR fetal survival.

Table 1.

Low birthweight animals exhibit multi-tissue pathologies that alter nutrient partitioning and contribute to inefficient growth and metabolism.

Low Birthweight Pathology	Potential Underlying Mechanism
Skeletal Muscle	
↓ Myoblast Function	↓ β_2 - to - β_1 Adrenergic Activity
↓ Hypertrophic Growth	↑ Inflammatory Sensitivity / Responsiveness
↓ Glucose Oxidation	Fiber Type Ratios
↓ Protein Accretion	
Adipose Tissue	
↑ Visceral Fat Deposition	↑ Macrophage Infiltration
↑ Adipocyte proliferation	↑ PPAR γ
	↑ Lipogenic Proteins
	↑ Nutrient Delivery
Liver	
↓ Mass	↓ Nutrient-Sensing Proteins (AMPK, mTOR, SIRT1)
↑ Triglyceride Accumulation	↑ Hepatic Inflammation
? Gluconeogenesis	↓ Fatty Acid Oxidation
Pancreatic β -cells	
↓ Glucose-Stimulated Insulin Secretion	Adrenergic Regulation
↓ Insulin Production	↓ Glucose Oxidation