The Effects of Developmental Programming upon Neonatal Mortality

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KEYWORDS

• Fetal programming • Calf • Neonate • Neonatal mortality

KEY POINTS

- The maternal environment (nutrition and physiologic status) can influence neonatal mortality and morbidity.
- The effects of gestational nutrition on birth weight, dystocia, and calf survival vary with the timing and duration of dietary interventions and the sex of the offspring.
- The ability to thermoregulate, stand, suckle, and ingest sufficient quantities of colostrum is critical to neonate survival and may be altered by in utero environment.
- The quantity of colostral immunoglobulins ingested by the neonate may be affected by prenatal ambient temperature and gestational diet.
- Gestational dietary restriction may alter thyroid function and diminish brown adipose tissue capacity concomitantly effecting lymphoid atrophy and neonatal immune function.

INTRODUCTION

The greatest loss in ruminant production systems occurs during the neonatal period, that is, between birth and 28 days of life. In extensive production systems, neonatal losses are reportedly between 10% and 30% and 6% and 16% for lambs and calves,

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respectively.[1,2] With 90% of these offspring born alive, this is considered a preventable welfare issue[1] and a high economic burden to the livestock industry.

It is well established that in utero environment[3] affects ruminant progeny health and welfare. This phenomenon is known as fetal programming and is contingent upon the particularly long gestation period in ruminants during which physiologic systems develop, such that at birth, the ontogeny of these systems is complete. The effects of this fetal programming in the neonate may be mediated by epigenetic modifications that regulate gene expression in both the placenta and the fetus[4] (**Fig. 1**). These epigenetic modifications may occur as early as embryogenesis[5] through to late gestation.[6] The placenta mediates fetal supply of nutrients, hormones, and oxygen[7,8] with both the placenta and the fetus responding to maternal perturbations in a sexually dimorphic manner.[9,10] This dimorphism has significant consequences because survival in the male fetus, during gestation and at birth, is reduced[11] compared with the female fetus.

Significantly for this review, many of the contributing factors associated with increased risk of neonatal mortality, that is, premature birth,[12] birth weight,[13] dystocia,[14,15] and poor adaptation to the postnatal environment,[16,17] are consequent to the prevailing prenatal environment.[3] Moreover, neonatal appetite, adiposity, and

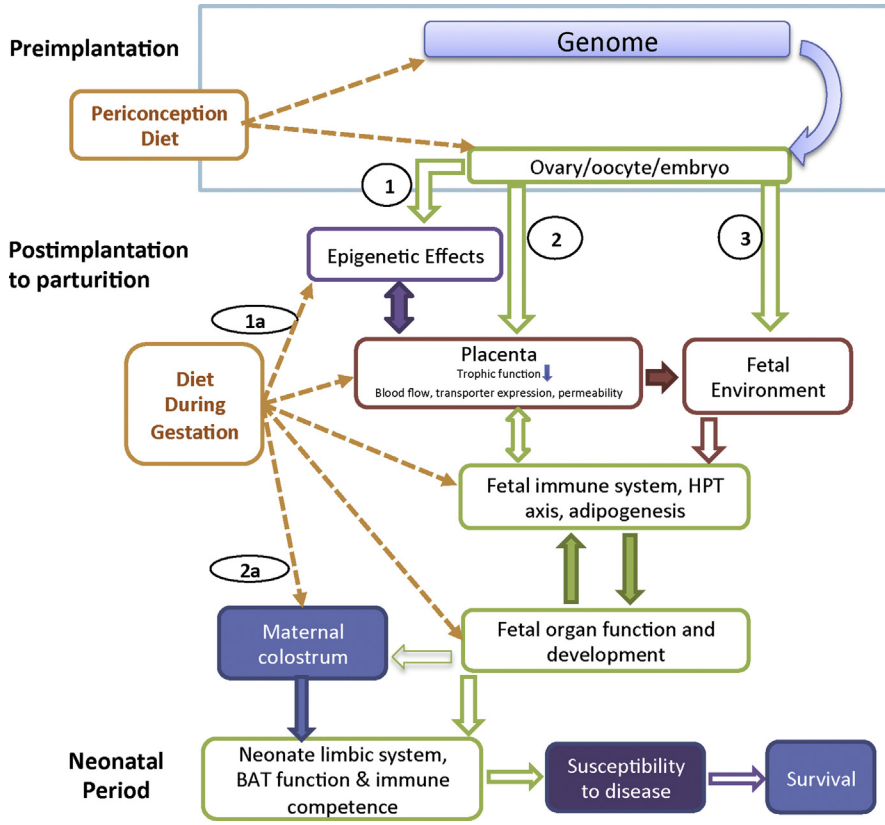


Fig. 1. (*1*) Fetoplacental unit responds to nutrient intake. (*1a*) Epigenetic changes in fetoplacental genes in response to nutrition. (*2*) Blood flow to the placenta and transporter changes affect placental permeability and function. (*2a*) Gestational diet alters colostrum quality (Immunoglobulins) and quantity. (*3*) Placental hormonal output modulates fetal environment.

immune function may be influenced by gestational diet in cattle[18,19] and sheep.[20] In this review, the authors address those aspects of neonatal mortality affected by fetal programming with particular reference to the bovine.

BIRTH WEIGHT, DYSTOCIA, AND NEONATAL SURVIVAL

Dystocia is the main cause of neonatal calf mortality,[14,21] either directly or indirectly via decreased vigor.[22] Calves that survive dystocia are reported to experience lower passive immunity transfer and increased risk of postnatal morbidity and mortality[23] and display higher indicators of physiologic stress.[11]

The incidence of dystocia in nulliparous beef heifers is higher than in multiparous cows,[13,24] despite birth weight of first parity progeny generally being lower.[25] High birth weight sufficient to cause dystocia is the major cause of neonatal calf loss.[22,26] A disproportionately large calf is the major contributor to dystocia in heifers,[23,24] with calf birth weight[27] and heifer size[15] considered the primary factors causing this fetal-maternal disproportion. In growing heifers, particularly those calving at 2 years of age, there is greater nutrient competition between the dam and rapidly developing fetus. They are effectively an adolescent[28] and display a greater response to dietary restriction compared with adults[29] similar to that observed in the ewe.[30] However, both low- and high-birth-weight extremes may be caused by dietary perturbations during gestation with extremely low-birth-weight calves also showing increased susceptibility to morbidity in cold climates[31] as observed in the lamb. Intriguingly, cold climate temperatures during gestation may be sufficient in themselves to reduce birth weight.[32]

As illustrated in **Table 1**, the timing of dietary interventions impacts the observed effect on birth weight: Interventions imposed before 100 days postconception (dpc), although causing greater effects on fetal organ development,[33] generally result in similar birth weights at term.[34] Nutrient restriction during the second trimester, however, may have the greatest influence on calf birth weight[2,29,35] sufficient to influence dystocia and thereby survival in the neonate.

Dietary interventions aimed at reducing birth weight and dystocia during the third trimester have produced varied responses.[25,36–39] This variation appears to be dependent on the severity of maternal weight loss.[29] However, this effect is generally not associated with reductions in dystocia perhaps due to increased length of second-stage labor.[15] In contrast, studies in sheep show maternal undernutrition[40] or overnutrition[41] in late pregnancy may reduce lamb birth weight with this effect commensurate with the level of weight change in the ewe.[3]

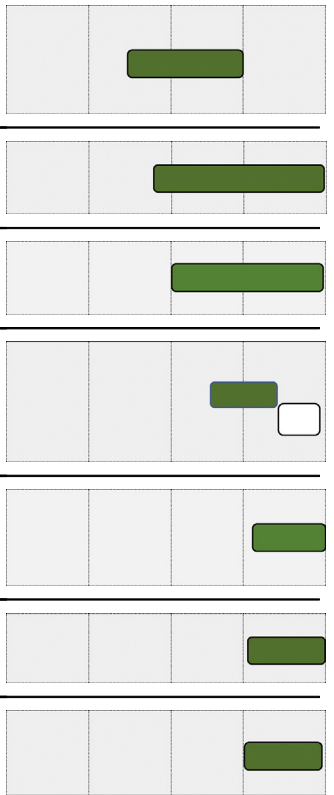
There is a sex-specific variation in dystocia rates in cattle, with greater occurrence typically associated with male offspring experiencing increased dystocia, neonatal morbidity, and mortality concomitant with their heavier birth weight[48] and placental dysfunction.[11] This effect is commensurate with the observed greater effect of early gestational perturbation to male fetal and placental growth and uterine hemodynamics.[9,10,28] Reductions in birth weight have also been observed following heat stress[49] and individual dietary nutrient restrictions.[2,45,50,51] Protein supplementation in mid to late gestation has been reported to have either no effect on birth weight[39,45,52,53] or an increased calf birth weight when cows graze low-quality winter pasture.[51] Protein supplementation during the second trimester in *Bos indicus* heifers increased birth weight by 8% while increasing dystocia rates 3-fold.[2]

Table 1 illustrates that the effects of maternal nutrient restriction during gestation on calf birth weight and dystocia vary dependent on age and parity of the dams studied, the nutritional regimens, and the timing of perturbation.[2,14,38] This table effectively clarifies the importance of timing and duration of gestational intervention,

Table 1
The effects of gestational dietary interventions on fetal development, birth weight, and dystocia

Refs	Dam Parity (Hf = Heifer & C = Cow)	n =	Period of Intervention (Days to Conception)	Treatment	Effects of Treatment on (L Compare with H or Control)					Pregnancy Stage/Trimester (Days Relative to Conception)			
					Sex	Placenta	Fetal	Birth Weight	Dystocia	Pre (−60 d)	First (0–90 d)	Second (90–180 d)	Third (>181 d)
Hernandez-Medrano et al,[9] 2015; Copping et al,[28] 2014	Hf	120	−60 d to 23 d & 24–90 d *2 × 2 Factorial design*	L = 7% CP[b] vs H = 14% CP[b]	Y (M > F)	↑ MUA blood flow	↓ wt (98 d) & ↓ CRL (32 d)	=	=				
Mossa et al,[33] 2013	Hf	23	−11 d to 110 d RA: 110 d to term	*Female only*[a] L = 60% E Mreq[a] vs H = 120% E Mreq[a] RA: 140% E Mreq[a]		NA		=	=				
Sullivan et al,[8] 2009; Micke et al,[2] 2010	Hf	120	0–93 d & 94–180 d *2 × 2 Factorial design*	L = 4% CP[b] vs H = 13% CP[b]	Y	NA	↓ CRL (36 d)	= (1st) ↓ (2nd)	↓				
Miguel-Pacheco et al,[35] 2016	Hf	80	14–90 d & 90–180 d *2 × 2 Factorial design*	L = 6% CP[b] & vs H = 16% CP[b] (RA)	Y (F > M)	NA	NA	↓	=				
Meyer et al,[42] 2010; Vonnahme et al,[43] 2007	C	40	30–125 d with RA: 125–220 d	*Female only*[a] L = 68% Mreq (9.9% CP) vs Ct = 100% Mreq (12% CP) RA (13.2% CP)		↓ wt (cotyl + carunc) ↓ vascularity (cotyl)	↓wt (125 d) but = (after RA) & ↑ GI tract	NA	NA				

Perry et al,[44] 1999	Hf	16	42–90 d & 90–180 d	L = 7% CP[b] vs H = 14% CP[b] *2 × 2 Factorial design*		↑ cotyl wt (LL/LH) & ↑ troph vol (LH/HL)	NA	=	=
Anthony et al,[39] 1986	Hf	59	75 d to term	L = 81% Mreq vs H = 141% Mreq (CPreq)		NA	NA	=	NA
Freetly et al,[29] 2000	C	144	90 d to term	28 kg wt loss			NA	↓	NA
Summers et al,[45] 2015	Hf	114	167–226 d	Isocaloric and isonitrogenous with L = 34% RUP vs H = 59% RUP RA	N	NA	NA	=	=
Bellows et al,[46] 1978	Hf & C		190 d to term	L = 3.2–3.4 kg TDN vs H = 6.3–6.4 kg TDN		NA	NA	↓ (Hf only)	↓
Tudor,[47] 1972	Hf & C	79 (Hf = 36 & C = 43)	180 d to term	L = 12.5% CP[a] vs H = 14.4% CP[a]		NA	↓ pregnancy length	↓	=
Corah et al,[48] 1975	Hf	59	180 d to term	L = 65% Mreq[a] vs H = 100% Mreq[a]		N/A	N/A	↓ (2 kg)	=



Abbreviations: ↑, increase; ↓, decrease; =, no effect; carunc, caruncle; cotyl, cotyledon; CP, crude protein; CRL, crown-rump length; E, energy; F, female; Green block, intervention period; H, high; L, low; M, male; Mreq, maintenance requirement according to NRC([a]) or ARC([b]); MUA, mid-uterine artery; NA, variable not measured/tested; N, no; RA, realimentation; RUP, rumen undegradable protein; troph, trophectoderm; white block, realimentation period; wt, weight; 1st, first trimester of pregnancy; 2nd, second trimester of pregnancy; Y, yes.

severity of the intervention, and sex of the offspring in the neonatal phenotype at birth.

NEONATAL ADAPTATION

Neonatal survival is dependent on the ability of the neonate to adapt rapidly to the ex utero environment. Sequentially, the ability to thermoregulate, stand, suckle, and ingest sufficient quantities of colostrum in the first hours of life is required.[54]

A calf's ability to thermoregulate is largely determined by the function of brown adipose tissue (BAT). BAT constitutes only 2% of body fat at birth but provides 50% of thermogenic response as nonshivering thermogenesis.[55] Adipogenesis, as with myogenesis and organogenesis, is complete in cattle and sheep before birth as it is in the human.[56] It is not surprising therefore that adipose tissue, including BAT, is significantly influenced by prenatal diet.[18,57,58] Adipose tissue has an important regulatory and homeostatic function particularly in the neonate.[59] BAT produces heat at 300 W/kg compared with 1 W/kg of in all other tissues,[60] by expressing a BAT-specific gene called uncoupling protein 1 (UCP1), which dramatically increases fuel oxidation.[61] One critical process in ensuring maximal activation of BAT is intracellular conversion of the thyroid hormone thyroxine to its active form, triiodothyronine (T3), by the enzyme 5′monodeiodinase type 2.[62] Thermoregulation and overall neonatal survival are influenced by the interaction between thyroid hormones, deiodinases, and BAT.[63] Restricted maternal diet during pregnancy has been shown to increase levels of thyroid hormones in the neonate, which may be able to upregulate UCP1 expression, acting to increase thermogenesis.[10] This increased thermogenesis may be a mean by which low-birth-weight calves can increase heat production. Interestingly, in rats, low-birth-weight offspring have raised UCP1 compared with normal-sized litter mates.[64]

As the fetal thyroid gland differentiates between 75 and 90 dpc, maternal dietary restriction during early gestation may reset the physiology of the hypothalamic–pituitary–thyroid (HPT) axis by altering ontogeny of the thyroid.[65] This altered ontogeny may act to increase free T3 (FT3) levels observed in the neonatal calf[10] and lamb.[66] As reported in lambs,[66,67] this increased FT3 may contribute to the "catch-up growth" of these low-birth-weight calves,[68] particularly because FT3 was positively correlated with average daily weight gain and fetal growth rate in calves in this study.[10]

Feeding behavior at birth is fundamental to calf survival, with the licking of the cow first stimulating the calf to stand and suckle.[69] This licking initiates the bond between mother and offspring.[70] Dairy calves take an average of 90 minutes to stand after birth and up to 6 hours to suckle for the first time,[69,71,72] whereas beef calves take up to 2 hours.[73] This time to first standing influences colostrum intake within the first 24 hours after birth.[74,75] Calves that take longer to stand will take longer to suckle,[71] potentially delaying the passive transfer of immunity and the provision of energy in the initial hours after birth.

Cows with highly responsive calves are more likely to provide maternal care,[76] which is important in free-ranging animals. The ability of a calf to stand and suckle is influenced by calf birth weight, sex, and ease of calving.[11] Periconception and first-trimester restricted protein intake in heifers has been shown to affect neonatal behavior of offspring.[77] Calves from heifers fed a low protein diet before conception showed higher duration of suckling behavior[77] sufficient to increase milk output.[78,79] Low-birth-weight calves have been reported to stimulate nursing bouts more frequently than calves with a higher birth weight.[76] This enhanced appetite may be prenatally programmed as neural pathways that are pivotal to appetite and voluntary food intake, which develop early in fetal ruminant life.[80] Gestational

dietary restriction alters gene expression for primary appetite regulating hypothalamic neuropeptides[81] and thereby appetite in the neonate.

NEONATAL IMMUNE FUNCTION

Ontogeny of the bovine immune response is parallel to the human because of similar gestational periods[82] with differentiation complete by the end of the first trimester. Three critical windows of vulnerability exist during the first trimester of gestation[83]: the period of embryonic stem cell formation, fetal liver development as the primary hematopoietic organ, and colonization and establishment of bone marrow and thymus. In the calf, lymphoid development of the thymus is complete at 42 dpc, with the spleen structurally present at 55 dpc, and peripheral and mesenteric lymph nodes at 60 dpc and 100 dpc, respectively. Thymic and splenic indices reach maximal values from 205 dpc. Therefore, the thymus has been suggested as the mediator of the effects of early gestational perturbation upon immune function in neonates.[84,85] Copping and colleagues[84] report that fetal thymus size and antibiotic use in the neonate may be altered by protein restriction early in gestation concomitant with effects upon colostral immunoglobulins.[10]

Allied with BAT's role in thermogenesis is the relationship with the function of neonatal immune and lymph systems. Prenatal dietary restriction may alter both thyroid function (as above) and diminish BAT capacity,[86] concomitantly effecting lymphoid atrophy.[87] Lymphoid tissues are susceptible to in utero perturbations early in gestation as thymic differentiation occurs by 42 dpc in the calf (similar to the human[88]) with other lymphoid structures present by 100 dpc.[82] BAT depots surround lymphoid tissues (including the thymus) in neonatal calves and lambs. It is proposed that they act not only as a dedicated lipid resource fueling immune activation in lymph nodes[89] but also to provide key fatty-acid, cellular, and adipokine immunoregulatory material that supports and regulates local immunity.[90] BAT located around the prescapular lymph node and sternal areas leading to the thymus is abundant in the neonatal calf[91] as it is in the lamb.[58] This BAT depot exhibits a different gene expression profile to perirenal BAT but may equally be susceptible to in utero intervention.[58,92] Interestingly, cattle breeds with better neonatal cold survival have increased expression of genes associated with BAT and immune function.[93,94]

Late gestational stressors, such as heat,[95] disease, drought,[21] or even dystocia,[11] may also affect immune function in the neonatal calf. The mechanisms driving this effect may include a reduction in food intake during the prenatal stress period. Nutritional supplementation with methionine, in combination with a high-energy diet, during the last trimester of pregnancy causes a decreased inflammatory response in the neonatal calf, by modulation of cellular responses.[96] These stress or nutritional interventions are thought to affect the calf via changes in cellular interactions with pathogens (CD18 and CD14) and changes in acute phase cytokines and pathogen recognition.[54]

Acquisition of passive immunity via colostral immunoglobulins in the first 24 hours of life[97–99] is required for calf survival.[100–102] The quantity of colostral immunoglobulin ingested is affected by dam age, prenatal ambient temperature,[96] and gestational diet.[103–105] Timing, severity, and period of prenatal intervention modify the observed affect.

Cows restricted from 90 dpc to term show immunoglobulin G (IgG) concentrations double that compared with cattle on a high plane of nutrition.[106] The latter effect may occur as the cow attempts to maintain transfer of passive immunity in the face of restricted diet.[106] Increased ambient temperatures late in gestation may decrease colostral IgG and IgA.[105]

Primiparous heifers may produce less colostrum with lower concentration of immunoglobulins compared with multiparous cows.[104] Calves from such heifers, however,

have been reported to have higher antibody concentrations despite lower levels of immunoglobulins being present in the colostrum.[107] This adaptation may be associated with necessity considering the lower birth weight of primiparous heifer calves.

SUMMARY

The authors have illustrated that the prenatal period influences neonatal mortality. Nutrient restriction, protein restriction, elevated ambient temperature, or a stress event during gestation may affect neonatal survival. This effect upon the neonate occurs by influencing a) Dystocia, both via increasing birth weight and placental dysfunction; (b) Thermoregulation, both via altering the amount of BAT and its ability to function via effects on the HPT axis; (c) Modification of the developing immune system and its symbiotic nutrient sources; (d) Modification of maternal and neonatal behavior. A lack of attention to these critical windows during prenatal life is hazardous to the commercial production of live calves.

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