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"The Effects of Developmental Programming upon Neonatal Mortality"

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Key Words: fetal programming, calf, neonate, neonatal mortality

Key Points:

- The maternal environment (nutrition and physiological status) can influence neonatal mortality and morbidity.
- The effects of gestational nutrition upon birthweight, 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 are 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 BAT capacity concomitantly effecting lymphoid atrophy and neonatal immune function.

Synopsis

The greatest loss in ruminant production systems occurs during the neonatal period. The maternal environment (nutrition and physiological status) influences neonatal mortality and morbidity as it reportedly affects; a) dystocia; both via increasing birthweight and placental dysfunction, b) neonatal thermoregulation; both via altering the amount of brown adipose tissue and its ability to function via effects upon the HPT axis, c) modification of the developing immune system and its symbiotic nutrient sources, d) modification of maternal and neonatal behavior.

Introduction

The greatest loss in ruminant production systems occurs during the neonatal period, i.e. between birth and 28d of life. In extensive production systems, neonatal losses are reportedly between 10-30% and 6-16% for lambs and calves, 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 physiological 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 which regulate gene expression in both the placenta and fetus [4] (Figure 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 fetus responding to maternal perturbations in a sexually dimorphic manner [9,10]. This has significant consequences as survival in the male, during gestation and at birth, is reduced[11] compared to the female.

Significantly for this review, many of the contributing factors associated with increased risk of neonatal mortality, i.e. premature birth[12], birthweight[13], dystocia[14,15] and poor adaptation to the postnatal environment[16,17], are consequent to the prevailing prenatal environment[18]. Moreover, neonatal appetite, adiposity and immune function, may be influenced by gestational diet in cattle [19,20] and sheep [21]. In this review, we will address those aspects of neonatal mortality affected by fetal programming with particular reference to the bovine.

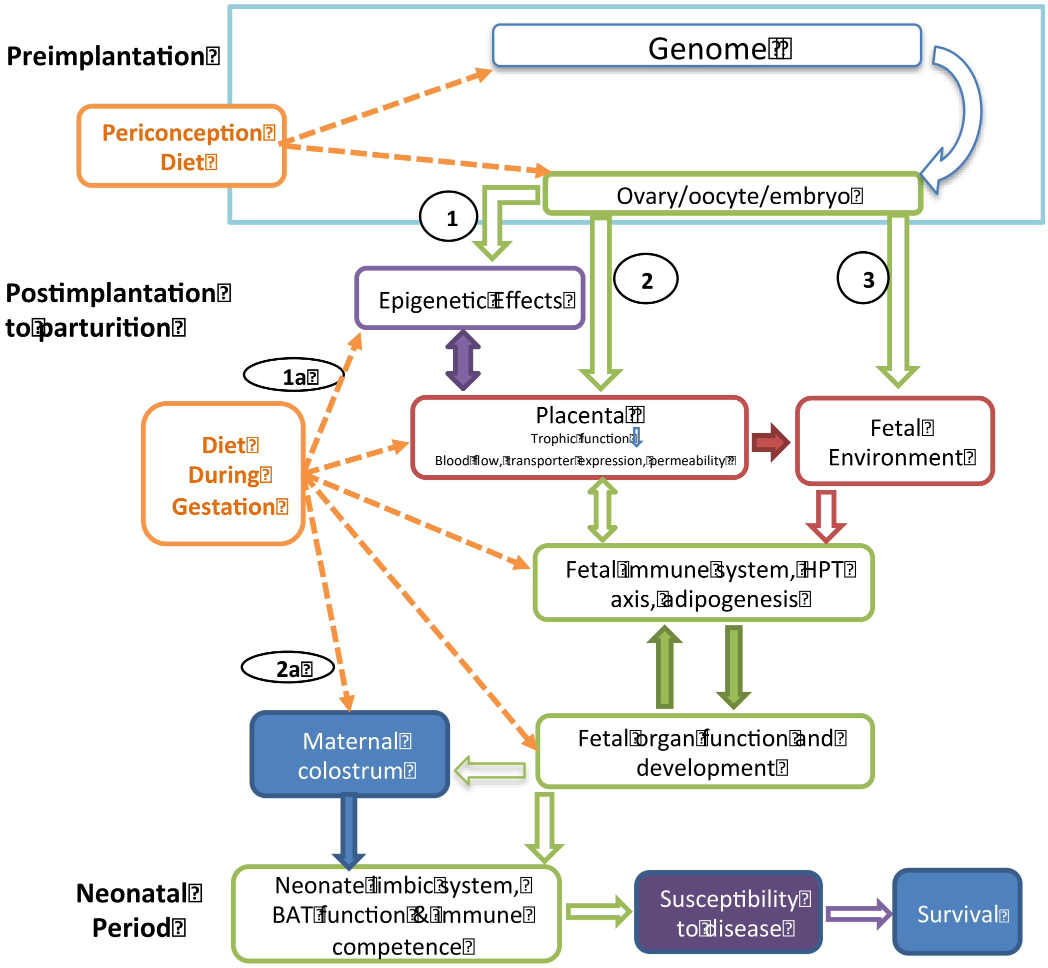


Figure 1. Effects of nutritional perturbation in the heifer upon the neonate. 1 feto-placental unit responds to nutrient intake, 1a: Epigenetic changes in feto-placental genes in response to nutrition; 2 blood flow to the placenta and transporter changes affect placental permeability and function 2a Gestational diet alters colostrum quality (Igs) and quantity; 3 Plancental hormonal output modulates fetal environment.

Birthweight, dystocia and neonatal survival

Dystocia is the main cause of neonatal calf mortality[14,22] either directly, or indirectly, via decreased vigour [23]. Calves which survive dystocia are reported to experience lower passive immunity transfer, increased risk of postnatal morbidity and mortality[24], and display higher indicators of physiological stress[11].

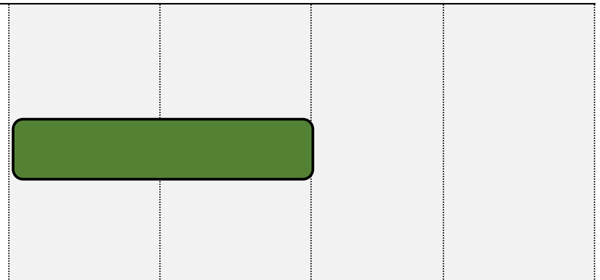
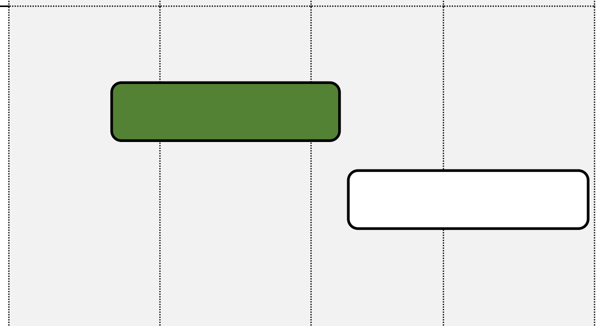
The incidence of dystocia in nulliparous beef heifers is higher than in multiparous cows[13,25], despite birthweight of first parity progeny generally being lower[26]. High birthweight sufficient to cause dystocia is the major cause of neonatal calf loss [23,27]. A disproportionately large calf is the major contributor to dystocia in heifers [24,25] with calf birthweight[28] and heifer size[15] considered the primary factors causing this fetal-maternal disproportion. In growing heifers, particularly those calving at two years of age, there is greater nutrient competition between the dam and rapidly developing fetus. They are effectively an adolescent [29] and display a greater response to dietary restriction compared to adults[30] similar to that observed in the ewe.[31] However, both low and high birthweight extremes may be caused by dietary perturbations during gestation with extremely low birthweight calves also showing increased susceptibility to morbidity in cold climates [32] as observed in the lamb. Intriguingly, cold climate temperatures during gestation may be sufficient in themselves to reduce birthweight[33].

As illustrated in Table 1, the timing of dietary interventions impacts the observed effect upon birthweight: Interventions imposed prior to 100 days post-conception (dpc), although causing greater effects upon fetal organ development[34], generally result in similar birthweights at term [35,36]. Nutrient restriction during the second trimester, however, may have the greatest influence on calf birthweight[30] [2,37] sufficient to influence dystocia and thereby survival in the neonate.

Dietary interventions aimed at reducing birthweight and dystocia during the third trimester have produced varied responses [26,38-41]. These appear to be dependent upon the severity of maternal weight loss [30]. However, this effect is generally not associated with reductions in dystocia perhaps due to increased length of second stage labour [42]. In contrast, studies in sheep show maternal undernutrition[43] or over nutrition[44] in late pregnancy may reduce lamb birthweight with this effect commensurate with the level of weight change in the ewe[3].

Table 1. The effects of gestational dietary interventions upon fetal development, birthweight and dystocia

Legend: Green block= period of intervention, white block= re-alimentation period, NA= variable not measured/tested,= no effect; ↓ = decrease; ↑ = increase, RUP = rumen undegradable protein, Mreq: Maintenance requirement according to NRC(†) or ARC(‡); E: energy; CP: crude protein.

Refs	Dam Parity (Hf=heifer & C=cow)	n =	Period of intervention (days to conception)	Treatment	Effects of treatment on (L compare to H or control)					Pregnancy stage / trimester (days relative to conception)			
					Sex	Placenta	Fetal	Birthweight	Dystocia	Pre (-60d)	First (0-90d)	Second (90-180d)	Third (>181d)
Hernandez-Medrano (2015)[9] & Copping et al (2014)[29]	Hf	120	-60d to 23d & 24 to 90d *2x2 Factorial design*	L= 7%CP‡ vs H= 14%CP‡	Y (M>F)	↑ MUA blood flow	↓ wt (98d) & ↓ CRL (32d)	=	=				
Mossa et al (2013)[34]	Hf	23	-11d to 110d RA: 110d to term	**Female Only.** † L= 60% E Mreq† vs H= 120% E Mreq† RA: 140% E Mreq†		NA		=	=				
Sullivan et al (2010)[8] & Micke et al (2010)[2]	Hf	120	0 to 93d & 94 to 180d *2x2 Factorial design*	L= 4%CP‡ vs H=13%CP‡	Y	NA	↓ CRL (36d)	= (1st) ↓ (2nd)	↓				

Refs	Dam Parity (Hf=heifer & C=cow)	n =	Period of intervention (days to conception)	Treatment	Effects of treatment on (L compare to H or control)					Pregnancy stage / trimester (days relative to conception)			
					Sex	Placenta	Fetal	Birthweight	Dystocia	Pre (-60d)	First (0-90d)	Second (90-180d)	Third (>181d)
Miguel-Pacheco et al (2016)[37]	Hf	80	14 to 90d & 90 to 180d *2x2 Factorial design*	L= 6% CP‡ & vs H= 16% CP‡ (RA)	Y (F>M)	NA	NA	↓	=				
Meyer et al 2010[45] & Vonnahme et al (2007)[46]	C	40	30 to 125d with RA: 125 to 220d	**Female Only**. † L= 68% Mreq (9.9%CP) vs Ct= 100% Mreq (12%CP) RA (13.2%CP)		↓ wt (cotyl+carunc) ↓ vascularity (cotyl)	↓wt (125d) but = (after RA) & ↑ GI tract	NA	NA				
Perry et al (1999)[47]	Hf	16	42 to 90d & 90 to 180d	L=7%CP‡ vs H=14%CP‡ *2x2 Factorial design*		↑ cotyl wt (LL/LH) & ↑ troph vol (LH/HL)	NA	=	=				
Anthony et al (1986)[48]	Hf	59	75d to term	L=81% Mreq vs H= 141% Mreq (CPreq)		N/A	N/A	=	NA				
Freetly et al (2000)[30]	C	144	90d to term	28kg wt loss			NA	↓	NA				

Refs	Dam Parity (Hf=heifer & C=cow)	n =	Period of intervention (days to conception)	Treatment	Effects of treatment on (L compare to H or control)					Pregnancy stage / trimester (days relative to conception)			
					Sex	Placenta	Fetal	Birthweight	Dystocia	Pre (-60d)	First (0-90d)	Second (90-180d)	Third (>181d)
Summers et al (2015)[49]	Hf	114	167 to 226d	Isocaloric and isonitrogenous with L=34% RUP vs H=59% RUP RA	N	NA	NA	=	=				
Bellows et al (1978)[50]	Hf & C		190d to term	L= 3.2-3.4kg TDN vs H=6.3-6.4kg TDN		NA	NA	↓ (Hf only)	↓				
Tudor (1972)[51]	Hf & C	79 (Hf=36 & C=43)	180d to term	L= 12.5%CP† vs H =14.4%CP†		NA	↓ pregnancy length	↓	=				
Corah et al (1975)[52]	Hf	59	180d to term	L=65% Mreq† vs H=100% Mreq†		N/A	N/A	↓ (2kg)	=				

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 birthweight[52] and placental dysfunction[11]. This is commensurate with the observed greater effect of early gestational perturbation to male fetal and placental growth and uterine hemodynamics [9,10,29]. Reductions in birthweight have also been observed following heat stress[53] and individual dietary nutrient restrictions[54-57]. Protein supplementation in mid- to late gestation has been reported to have either no effect on birthweight [41,57-59] or increase calf birthweight when cows graze low-quality winter pasture [56]. Protein supplementation during the second trimester in *Bos indicus* heifers increased birthweight by 8% while increasing dystocia rates three fold [55].

Table 1 illustrates effects of maternal nutrient restriction during gestation upon calf birthweight and dystocia vary dependent upon age and parity of the dams studied, the nutritional regimens and the timing of perturbation [14,40,55]. This effectively clarifies the importance of timing and duration of gestational intervention, severity of the intervention and sex of the offspring in the neonatal phenotype at birth.

Neonatal adaptation

Neonatal survival is dependent upon 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[60].

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 non-shivering thermogenesis[61]. Adipogenesis, as with myogenesis and organogenesis, is complete in cattle and sheep prior to birth as it is in the human[62]. It is not surprising therefore that adipose tissue, including BAT, is significantly influenced by prenatal diet[19,63,64]. Adipose tissue has an important regulatory and homeostatic function particularly in the neonate [65]. BAT produces heat at 300 W/kg compared with 1W/kg of in all other tissues[66], by expressing a BAT-specific gene called uncoupling protein (UCP)1 which dramatically increases fuel oxidation[67]. One critical process in ensuring maximal activation of BAT is intra-cellular conversion of the thyroid hormone thyroxine (T4) to its active form,

triiodothyronine (T3), by the enzyme 5'monodeiodinase type 2 (DIO2)[68]. Thermoregulation and overall neonatal survival is influenced by the interaction between thyroid hormones, deiodenases and BAT[69]. Restricted maternal diet during pregnancy has shown to increase levels of thyroid hormones in the neonate which may be able to upregulate UCP1 expression, acting to increase thermogenesis.[10] Suggested as a means by which low birthweight calves can increase heat production. Interestingly, in rats, low birth weight offspring have raised UCP1 compared to normal sized litter mates[70].
As fetal thyroid gland differentiates between 75 and 90 dpc, maternal dietary restriction during early-gestation may reset the physiology of the HPT axis by altering ontogeny of the thyroid[71]. This is reflected in increased free T3 (FT3) levels in the neonatal calf[10] and lamb[72]. As reported in lambs [72,73], this increased FT3 may contribute to the "catch-up growth" of these low birth weight calves [74] particularly as FT3 was positively correlated with average daily weight gain and fetal growth rate in calves in this study[10].

Feeding behaviour at birth is fundamental to calf survival, with the licking of the cow first stimulating the calf to stand and suckle[75]. This initiates the bond between mother and offspring[76]. Dairy calves take an average of 90 min to stand after birth and up to 6hrs to suckle for the first time[75,77,78], whereas beef calves take up to 2 hrs[79]. This time to first standing influences colostrum intake within the first 24 hours after birth[80,81] . Calves that take longer to stand will take longer to suckle[77], 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[82], 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 behaviour of offspring[83]. Calves from heifers fed a low protein diet before conception showed higher duration of suckling behaviour[83] sufficient to increase milk output [84] [85]. Low birth weight calves have been reported to stimulate nursing bouts more frequently than calves with a higher birth weight [82]. 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[86]. Gestational dietary restriction alters gene expression for primary appetite regulating hypothalamic neuropeptides [87] and thereby appetite in the neonate.

Neonatal immune function

Ontogeny of the bovine immune response is parallel to the human due to similar gestational periods[88] with differentiation complete by the end of the first trimester. Three critical windows of vulnerability exist during the first trimester of gestation[89] ;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[90,91]. Copping et al., 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.[10,90]

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[92] concomitantly effecting lymphoid atrophy[93]. 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[94]) with other lymphoid structures present by 100dpc[88]. 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 fuelling immune activation in lymph nodes[95], but also to provide key fatty-acid, cellular and adipokine immunoregulatory material that support and regulate local immunity[96]. BAT located around the prescapular lymph node and sternal areas leading to the thymus is abundant in the neonatal calf [97] as it is in the lamb[64]. This BAT depot exhibits a different gene expression profile to perirenal BAT but may equally be susceptible to in utero intervention.[64,98]. Interestingly cattle breeds with better neonatal cold survival have increased expression of genes associated with BAT and immune function[99,100].

Late gestational stressors such as heat [101] , disease, drought [22], 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 decrease inflammatory response in the neonatal calf, by modulation of cellular responses **[102].** These stress or nutritional interventions are thought to effect the calf via changes in cellular interactions with pathogens (CD18 and CD14) and changes in acute phase cytokines and pathogen recognition [60]

Acquisition of passive immunity via colostral immunoglobulins (Ig) in the first 24hrs of life [103] [104] [105] is required for calf survival [106,107] [108]. The quantity of colostral Ig ingested is affected by dam age, prenatal ambient temperature[102] and gestational diet [109-111]. Timing, severity and period of prenatal intervention modifies the observed affect:

Cows restricted from 90dpc to term show IgG concentrations double that compared to cattle on a high plane of nutrition [112]. The latter effect may occur as the cow attempts to maintain transfer of passive immunity in the face of restricted diet [112]. Increased ambient temperatures late in gestation may decrease colostral IgG and IgA [111]. Primiparous heifers may produce less colostrum with lower concentration of Igs compared to multiparous cows[113]. Calves from such heifers, however, have been reported to have higher antibody concentrations despite lower levels of Ig being present in the colostrum[114]. This adaptation may be associated with necessity considering the lower birthweight of primiparous heifer calves.

Conclusion

We have illustrated that the prenatal period influences neonatal mortality. Total nutrient restriction, protein restriction, elevated ambient temperature, or a stress event, during gestation may affect neonatal survival. This occurs via affects upon; a) dystocia; both via increasing birthweight and placental dysfunction, b) thermoregulation; both via altering the amount of brown adipose tissue and its ability to function via effects upon the HPT axis, c) modification of the developing immune system and its symbiotic nutrient sources, d) modification of maternal and neonatal behaviour. A lack of attention to these critical windows during prenatal life is hazardous to the commercial production of live calves.

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