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Review: Importance of colostrum supply and milk feeding intensity on gastrointestinal and systemic development in calves

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Feeding management of the postnatal and preweaning calf has an important impact on calf growth and development during this critical period and affects the health and well-being of the calves. After birth, an immediate and sufficient colostrum supply is a prerequisite for successful calf rearing. Colostrum provides high amounts of nutrient as well as non-nutrient factors that promote the immune system and intestinal maturation of the calf. The maturation and function of the neonatal intestine enable the calf to digest and absorb the nutrients provided by colostrum and milk. Therefore, colostrum intake supports the start of anabolic processes in several tissues, stimulating postnatal body growth and organ development. After the colostrum feeding period, an intensive milk feeding protocol, that is, at least 20% of BW milk intake/day, is required to realise the calf potential for growth and organ development during the preweaning period. Insufficient milk intake delays postnatal growth and may have detrimental effects on organ development, for example, the intestine and the mammary gland. The somatotropic axis as the main postnatal endocrine regulatory system for body growth is stimulated by the intake of high amounts of colostrum and milk and indicates the promotion of anabolic metabolism in calves. The development of the forestomach is an important issue during the preweaning period in calves, and forestomach maturation is best achieved by solid feed intake. Unfortunately, intensive milk-feeding programmes compromise solid feed intake during the first weeks of life. In the more natural situation for beef calves, when milk and solid feed intake occurs at the same time, calves benefit from the high milk intake as evidenced by enhanced body growth and organ maturation without impaired forestomach development during weaning. To realise an intensive milk-feeding programme, it is recommended that the weaning process should not start too early and that solid feed intake should be at a high extent despite intensive milk feeding. A feeding concept based on intensive milk feeding prevents hunger and abnormal behaviour of the calves and fits the principles of animal welfare during preweaning calf rearing. Studies on milk performance in dairy cows indicate that feeding management during early calf rearing influences lifetime performance. Therefore, an intensive milk-feeding programme affects immediate as well as long-term performance, probably by programming metabolic pathways during the preweaning period.

Keywords: preweaning calf, somatotropic axis, nutrient intake, organ maturation, growth

Implications

Successful calf rearing depends on an enhanced colostrum management and is improved by an intensive milk-feeding programme that allows calves to develop their potential for growth and organ maturation. Feeding regimes with a restricted milk supply of 4 to 6 kg milk or milk replacer/ day focus on forestomach development and may disregard body growth and the maturation of other visceral organs beyond the rumen. An *ad libitum* milk-feeding programme stimulates calf growth and organ development and is consistent with calf well-being and avoids hunger. In addition, intensive milk feeding may have a strong impact on calf health and long-life performance in cattle.

Introduction

Mortality and morbidity rates are still unacceptably high during early calf rearing. The incidence for mortality in the perinatal period, defined as the duration from birth to 48 h after birth, ranges in dairy herds worldwide between 3% and 9% (Compton *et al.*, 2017). A recent survey on mortality

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rates in Germany revealed up to 17% calf losses (calf losses after birth up to 6 months of age) in dairy farms (Tautenhahn, 2017). In US dairy herds, current mortality rates of 5% and morbidity rates of 34% were published for preweaning calves (Urie et al., 2018). The UK Department of the Environment, Food and Rural Affairs reported that economic losses from calf mortality were around £60 million/year (DEFRA, 2003). It is obvious that the high mortality and morbidity rates contradict the aim of increased animal welfare for farm animals and compromise the breeding of robust animals (Huber, 2018). In dairy farming, calves usually do not grow up with their dam, and calves are immediately separated from their dams after birth. Thus, farmers are highly responsible for the colostrum and milk feeding management and can significantly contribute to an improved calf health and the reduction of calf losses during the postnatal period.

Feeding management during the neonatal and preweaning period has a great impact on the success of calf rearing and, in addition, affects health and performance in later life (Khan et al., 2011; Ballou, 2012; Van Amburgh and Soberon, 2013). Because severe diarrhoea is a main reason for neonatal calf losses, the management of milk feeding and especially colostrum supply in the first days of life is of particular importance for the success of calf rearing (DEFRA, 2003; Tautenhahn, 2017; Urie et al., 2018). An adequate and immediate (within 2 to 3 h after birth) colostrum supply is important for establishing passive immunity in calves, and the amount of colostrum fed to newborn calves directly correlates with the prevention of illness and calf losses (Godden, 2008; Mee, 2008).

Furthermore, there is increasing evidence that an enhanced milk or milk replacer (**MR**) feeding schedule during the preweaning period not only affects growth but also promotes organ development and well-being (Geiger et al., 2016; Schäff et al., 2016; Rosenberger et al., 2017). This review aims to summarise the research on the impact of colostrum supply and subsequent intensive milk feeding on the gastrointestinal and systemic development and maturation of the preweaning calf. An intensive milk feeding schedule orientates on a daily milk intake of 20% instead of 10% of BW (Khan et al., 2011), which is closely related to ad libitum milk (Jasper and Weary, 2002; Schiessler et al., 2002; Maccari et al., 2015) or MR feeding (Schäff et al., 2016; Frieten et al., 2017) in preweaning calves.

Impact of colostrum supply on postnatal maturation

Colostrum supply and intestinal development and maturation

Bovine colostrum provides newborn calves with high amounts of nutrient and non-nutrient biologically active substances (Blum and Baumrucker, 2008; Nissen et al., 2017). In addition to the great importance of colostral immunoglobulins for the passive immunity of neonatal calves (Barrington and Parish, 2001; Godden, 2008), colostrum contains a large number of immunomodulatory peptides that may also affect neonatal immune response (Chase et al., 2008; Stelwagen et al., 2009; Nissen et al., 2017). Some of these factors are provided by colostral immune cells that are involved in the establishment of local and systemic neonatal immunity (Liebler-Tenorio et al., 2002; Stelwagen et al., 2009; Langel et al., 2015). In addition, potential effects of colostrum on the neonatal microbiome in the gut are likely and become more important in the research of calf nutrition (Malmuthuge and Guan, 2017). The importance of the colostrum supply for the development and maturation of the immune system of the newborn calf is far beyond the provision of immunoglobulins. Recent studies in humans, investigating the effects of breastmilk feeding on neonatal intestinal development, illustrate the significance of colostral immune cells and the intestinal microbiome on the maturation of the neonatal immune response in the gut (Molès et al., 2018). A comparable function of bovine colostrum in the neonatal intestine of the calf is conceivable but requires more investigations.

Bovine colostrum has an overall importance for the postnatal development of the gut (Blum, 2006). The high concentrations of hormones, growth factors and cell-modulating factors in colostrum (Blum and Baumrucker, 2008; Nissen et al., 2017) stimulate villus growth of the small intestinal mucosa in calves (Blum, 2006; Steinhoff-Wagner et al., 2014). Colostrum feeding promotes mucosal cell growth and protein synthesis in the enterocytes of neonatal mammals (Donovan and Odle, 1994; Burrin et al., 1995; Xu, 1996). The amount of overall ingested colostrum corresponds to the villus size in the intestinal mucosa, leading to a greater villus size in repeatedly colostrum-fed calves (Blum, 2006). When feeding a colostrum extract, that is, a fraction originating from first colostrum including most of the growth-promoting peptides, together with a milk-based formula, the villus size is stimulated when compared to a milk-based formula feeding with similar protein and energy as in colostrum but no growth-stimulating peptides (Roffler et al., 2003). This finding supports the general assumption that colostral peptides, such as IGF-I, or hormones, such as insulin, are involved in the growth-stimulating effect on the intestinal mucosa of neonatal calves (Blum, 2006).

In general, the proliferation rate of intestinal crypt cells depends on feeding (Johnson 1988; Mathers, 1998). Colostrum or colostral components stimulate crypt cell proliferation in the intestinal mucosa of neonatal calves (Blum, 2006). When comparing colostrum feeding and milk-based formula feeding (same nutrient content but no growth-promoting bioactive factors as colostrum during the first 3 days after birth), the greater stimulation of cell proliferation corresponded to the greater villus growth in colostrum than formula-fed calves on day 8 of life (Blum, 2006). The cell turnover of the intestinal mucosa depends on cell proliferation and programmed cell death (apoptosis; mainly seen at the villus tips) (Ramachandran et al., 2000). Colostrum intake reduces apoptosis of epithelial cells and therefore prolongs the lifespan of the epithelial cells (Blum, 2006).

Milk-borne factors such as IGF-I are known for their stimulation of cell proliferation (Burrin *et al.*, 1996; Hammon *et al.*, 2013; Ontsouka *et al.*, 2016) as well as inhibition of cell death due to apoptosis or inflammation in the intestinal mucosa (Mylonas *et al.*, 2000; Blum, 2006). Recombinant human IGF-I, fed together with MR in neonatal calves, increases intestinal cell proliferation (Blum, 2006). A more distinct stimulation of mucosal cell proliferation is observed when feeding a colostrum extract (see above) instead of a single growth-promoting peptide (Roffler *et al.*, 2003). This finding indicates that not a single factor but the interaction of the large amount of growth-stimulating substances in the colostrum promotes intestinal cell proliferation and growth (Hammon *et al.*, 2012). Receptors for IGF-I, IGF-II and insulin (IGF1R, IGF2R and InsR, respectively) are present in the intestinal mucosa throughout the total gut in neonatal calves, and their expression and/or binding capacities are modified by colostrum feeding and orally administered rhIGF-I (Blum, 2006; Hammon *et al.*, 2013; Ontsouka *et al.*, 2016). The density of IGF1R and InsR, but not IGF2R, in the intestinal mucosa seems to be associated with crypt cell proliferation (Georgiev *et al.*, 2003).

Most biologically active factors in colostrum, such as IGF-I, IGF-II and insulin, are barely absorbed and therefore likely have no systemic function (Blum, 2006; Hammon *et al.*, 2013). Therefore, local effects of colostral factors on crypt cell proliferation, intestinal epithelial growth and intestinal maturation may dominate in neonatal farm animals (Donovan and Odle, 1994; Xu, 1996; Blum, 2006). However, recent findings in calves indicate the absorption of colostral adiponectin in neonatal calves (Kesser *et al.*, 2015), an adipokine involved in the regulation of insulin sensitivity (Kadowaki *et al.*, 2006). With respect to the lactocrine signalling theory described in pigs (Bartol *et al.*, 2013), the intestinal absorption of adiponectin may contribute to the stimulation of anabolic metabolism in neonatal calves after colostrum feeding (Hammon *et al.*, 2012). Colostrum feeding supports protein synthesis in the skeletal muscle of piglets (Burrin *et al.*, 1995), and the present research suggests a similar effect in neonatal calves, indicating enhanced protein synthesis in skeletal muscle due to insulin action after colostrum feeding (Hammon *et al.*, 2012; Sadri *et al.*, 2017). The impact of adiponectin on this finding, however, is not clear and needs further investigation.

Colostrum supply and glucose metabolism
Due to its growth-stimulating effect in the small intestine, colostrum intake promotes the absorptive capacity of the small intestine. Measurements of xylose and glucose absorption in neonatal calves clearly indicate a greater absorption after feeding with colostrum instead of formula or MR (Blum, 2006; Steinhoff-Wagner *et al.*, 2011; Gruse *et al.*, 2015). Xylose absorption on day 5 of age after feeding colostrum only once was similar to that after feeding colostrum for the first 3 days after birth (Hammon *et al.*, 2013). Therefore, the intake of first colostrum during the first hours after birth is of great importance for glucose absorption and

the postnatal glucose status in neonatal calves. In contrast, digestive enzymes and mucosal transporters with respect to carbohydrate digestion, such as lactase and SGLT1 and GLUT2, seem to be less affected by colostrum feeding. A distinct stimulation of lactase activity and the glucose transporter when feeding colostrum instead of a milk-based formula was barely observed in neonatal calves (Sauter *et al.*, 2004; Steinhoff-Wagner *et al.*, 2014). For more details concerning digestive enzymes in neonatal calves, readers are referred to Guilloteau *et al.* (2009a). Recent studies using metabolomics approaches in neonatal calves indicate that the uptake and metabolism of other nutrients (e.g. amino acids) are also influenced by colostrum feeding (Qi *et al.*, 2018; Zhao *et al.*, 2018).

First-pass glucose uptake in the splanchnic tissue on days 2 and 7 of life is greater in formula-fed than colostrum-fed calves, indicating a greater glucose utilisation in the splanchnic tissue (gastrointestinal tract and liver) of calves not fed with colostrum (Steinhoff-Wagner *et al.*, 2011; Gruse *et al.*, 2015). Possibly, nutrient absorption is generally impaired in formula-fed calves, leading to increased glucose utilisation in the splanchnic tissue, whereas colostrum-fed calves are able to use greater amounts of digested fat and protein as energy fuel in the splanchnic tissue. This hypothesis is supported by the finding that oral fat absorption is greater in colostrum- than in formula-fed or MR-fed calves, providing more fat (i.e. medium-chain fatty acids from colostrum) as energy fuel in the splanchnic tissue that partly can replace glucose utilisation (Hammon *et al.*, 2012). In contrast to intestinal glucose absorption, a stimulating influence of colostrum intake on endogenous glucose production, as supposed to be the case in piglets (Lepine *et al.*, 1991), does not occur in bovine neonates. Thus, growth-promoting substances of ingested colostrum do not affect endogenous glucose production in neonatal calves (Steinhoff-Wagner *et al.*, 2011). Nevertheless, the increased plasma glucose concentration and the greater hepatic glycogen content in colostrum-fed calves indicate an improved glucose status by colostrum feeding (Steinhoff-Wagner *et al.*, 2011; Hammon *et al.*, 2012 and 2013). These findings lead to the conclusion that the improved glucose status in calves fed colostrum immediately after birth and for 3 days is a result of enhanced glucose absorption and probably of less glucose utilisation in the splanchnic tissue but is not a result of increased endogenous glucose production.

Colostrum supply and maturation in the somatotropic axis
The elevated glucose availability and the improved insulin status in colostrum-fed calves are important prerequisites for the accelerated maturation of the somatotropic axis, as indicated by several studies in neonatal calves that were previously summarised (Blum, 2006; Hammon *et al.*, 2012). The stimulation of gastrointestinal hormones due to colostrum feeding may contribute to the elevated insulin secretion in the calves (Hadorn *et al.*, 1997; Inabu *et al.*, 2019). The elevated insulin status due to colostrum feeding in neonatal calves is probably the trigger for stimulating endogenous

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IGF-I and the postnatal somatotropic axis (Hammon *et al.*, 2012) because glucose and insulin stimulate the hepatic gene expression of the growth hormone receptor and IGF-I as well as IGF-I secretion (Brameld *et al.*, 1999; Butler *et al.*, 2003). On the other hand and as discussed earlier, studies in neonatal calves and piglets indicate no intestinal absorption of colostral IGF-I or insulin (Donovan *et al.*, 1997; Blum, 2006). Thus, the endogenously produced IGF-I determines the IGF-I status of the calf. Therefore, the nutrient supply is responsible for the maturation of the neonatal somatotropic axis, and the colostral IGF-I promotes intestinal development of the neonatal calf but does not contribute to systemic IGF-I availability (Blum, 2006; Hammon *et al.*, 2012; Ontsouka *et al.*, 2016).

In summary, the postnatal maturation of the neonatal intestine is enhanced due to colostrum intake, and the improved intestinal maturation results in a greater nutrient absorption and stimulation of anabolic processes that are a prerequisite for accelerated postnatal growth.

Development of the preweaning calf due to intensive milk feeding

Definition of intensive milk feeding

After the colostrum period, the calf depends on the intake of liquid feed in the form of milk or high-quality MR for nutrient supply. Although it is a common feeding strategy to increase solid feed intake as soon as possible in the preweaning period by reducing milk feeding (Huber, 1969; Gelsinger *et al.*, 2016; Kertz *et al.*, 2017), solid feed intake during the first 3 weeks of age is low, and the digestion of solid feed is impaired due to the immature forestomach in the postnatal period (Drackley, 2008; Khan *et al.*, 2016; Frieten *et al.*, 2017). Thus, sufficient milk or MR supply during the first weeks of life is a prerequisite for calf growth and development. The World Organisation for Animal Health (**OIE**) defines animal welfare in the Terrestrial Animal Health Code as a state where the animal is healthy, comfortable, well nourished, safe, able to express natural behaviour and not suffering from pain, fear and distress (OIE, 2017). Feeding calves limited amounts of liquid feed (i.e. 4 to 6 kg/day) during the first weeks of life results in a lack of expression in natural suckling behaviour (Schiessler *et al.*, 2002; Miller-Cushon and DeVries, 2015) followed by hunger (Jensen and Holm, 2003; De Paula Vieira *et al.*, 2008; Borderas *et al.*, 2009; Gerbert *et al.*, 2018) and stress for the calves. Allowing calves to drink unlimited amounts of milk or MR for several weeks during the preweaning period more than doubles liquid feed intake compared with restricted amounts of 4 to 6 kg/day of MR or milk (Hammon *et al.*, 2002; Maccari *et al.*, 2015; Schäff *et al.*, 2016; Frieten *et al.*, 2017). Therefore, an intensive milk-feeding programme contributes to the overall well-being of preweaning calves (Von Keyserlingk *et al.*, 2009; FAWC, 2015; OIE, 2017).

An intensive milk feeding provides milk or MR in unrestricted amounts all day long for 24 h. The calves have *ad libitum* access to milk (Jasper and Weary, 2002; Schiessler *et al.*, 2002; Maccari *et al.*, 2015) or MR feeding (Schäff *et al.*, 2016; Frieten *et al.*, 2017; Korst *et al.*, 2017) for several weeks. *Ad libitum* MR feeding (125 g powder/l, 21.7% CP and 18.3 MJ metabolisable energy (**ME**) per kg DM) provides on average 1.6 kg DM/day, 35 MJ ME/day and 347 g protein/day to the calves during the intensive milk-feeding period. In this context, daily peaks of more than 2 kg DM intake were observed in previous studies (Schäff *et al.*, 2016; Frieten *et al.*, 2017). Such feeding schedules provide much more protein and energy than commonly used milk-feeding programmes of 4 to 6 kg milk/day. *Ad libitum* milk-feeding programmes are comparable to early calf rearing in beef production where calves live together with their dams and have free access to milk all day long (Egli and Blum, 1998; Schiessler *et al.*, 2002). Main findings of an intensive milk feeding protocol compared to restricted milk feeding on calf growth, organ development, metabolic and endocrine changes, feeding behaviour and immune response have been summarised in Table 1.

Stimulation of growth and endocrine growth regulation by intensive milk feeding

Ad libitum milk or MR feeding (Maccari *et al.*, 2015; Schäff *et al.*, 2016; Korst *et al.*, 2017) or enhanced milk-feeding programmes using MR with a greater protein content (up to 30% CP in DM) (Smith *et al.*, 2002; Geiger *et al.*, 2016) resulted in an elevated body growth during the preweaning period when compared to restricted milk or MR feeding (4 to 6 kg milk or MR/day). In addition to stimulating muscle and fat growth (Bartlett *et al.*, 2006; Geiger *et al.*, 2016; Schäff *et al.*, 2016; Koch *et al.*, 2019), intensive milk or MR intake accelerates organ growth, for example, small intestine, mammary gland, thymus and endocrine pancreas (Prokop *et al.*, 2015; Geiger *et al.*, 2016; Soberon and Van Amburgh, 2017; Koch *et al.*, 2019). As discussed later in this review, the velocity of body growth could temporarily decrease in intensive milk-fed calves during the weaning process due to the adaptation to solid feed intake. However, BW at the end of the weaning process is still greater in intensively than restrictively milk-fed calves (Maccari *et al.*, 2015; Schäff *et al.*, 2016; Frieten *et al.*, 2017).

Studies on the hepatic transcriptome and proteome in lambs and metabolome in blood plasma of calves reveal marked changes with respect to protein and energy metabolism when animals receive MR *ad libitum* instead of in restricted amounts (Kenéz *et al.*, 2018; Santos *et al.*, 2019). In lambs, restricted MR feeding stimulates hepatic pathways involved in gluconeogenesis, amino acid degradation and hepatic fatty acid oxidation, which points at changes in energy utilisation to stabilise glucose homeostasis as compared to *ad libitum* MR-fed lambs (Santos *et al.*, 2019). In calves, *ad libitum* instead of restricted MR feeding seems to increase the capacity for mitochondrial transport of fatty acids and probably affects fatty acid oxidation as well (Kenéz *et al.*, 2018). In addition, an enhanced MR-feeding programme leads to a greater metabolic activity in muscle

Table 1 *Effects of intensive milk feeding immediately after birth on growth, development, behaviour and immune response in preweaning calves[1]*

Item effect due to intensive feeding when compared to restricted milk feeding	Type of intensive milk or milk replacer feeding[2]	Duration in weeks	Reference
Increased BW and body growth	*Ad libitum* feeding of milk powder	4	Hammon *et al.* (2002)
	Ad libitum feeding of whole milk	5	Jasper and Weary (2002)
	20% of BW/day of whole milk	3.5	Khan *et al.* (2007b)
	1.4 kg DM/day milk replacer with 27% CP and 28% crude fat	9	Daniels *et al.* (2009)
	2.1% of BW DM/day milk replacer with 30.6% CP and 16.1% crude fat	4	Davis Rincker *et al.* (2011)
	Ad libitum feeding of whole milk	3	Maccari *et al.* (2015)
	1.08 kg DM/day milk replacer with 28.9% CP and 26.2% crude fat	8	Geiger *et al.* (2016)
	Ad libitum feeding of milk replacer	5	Schäff *et al.* (2016)
	Ad libitum feeding of milk replacer	8	Frieten *et al.* (2017)
	Ad libitum feeding of milk replacer or whole milk	3.5	Korst *et al.* (2017)
Organ growth and development			
Elevated forestomach and rumen papillae growth postweaning	20% of BW/day of whole milk	3.5	Khan *et al.* (2007a)
	2% of BW DM/day milk replacer with 28.5% CP and 15% crude fat	5	Naeem *et al.* (2012)
No impairment on rumen development postweaning	*Ad libitum* feeding of milk replacer	5	Schäff *et al.* (2018)
	Ad libitum feeding of milk replacer	8	Koch *et al.* (2019)
Enhanced muscle and body fat growth	2% of BW DM/day milk replacer with 28.5% CP and 15% crude fat	5	Wang *et al.* (2014)
	Ad libitum feeding of milk replacer	5	Schäff *et al.* (2016)
Enhanced growth of the small intestine	*Ad libitum* feeding of milk replacer	8	Koch *et al.* (2019)
Enhanced growth and development of the mammary gland	1.4 kg DM/day milk replacer with 27% CP and 28% crude fat	9	Daniels *et al.* (2009)
	1.08 kg DM/day milk replacer with 28.9% CP and 26.2% crude fat	8	Geiger *et al.* (2016)
	1.24 MJ/kg BW$^{0.75}$ per day milk replacer with 28.5% CP and 15% crude fat	8	Soberon and Van Amburgh (2017)
Stimulation of the endocrine pancreas secretion	*Ad libitum* feeding of whole milk	3	Prokop *et al.* (2015)
Metabolic and endocrine changes			
Systemic metabolic changes indicating greater metabolic activity	*Ad libitum* feeding of milk replacer	5	Schäff *et al.* (2016)
	Ad libitum feeding of milk replacer	8	Frieten *et al.* (2017)
	Ad libitum feeding of milk replacer or whole milk	3.5	Kenéz *et al.* (2018)
Elevated plasma insulin and stimulation of the somatotropic axis	20% of BW/day of whole milk	3.5	Khan *et al.* (2007a)
	1.4 kg DM/day milk replacer with 27% CP and 28% crude fat	9	Daniels *et al.* (2008)
	Ad libitum feeding of whole milk	3	Maccari *et al.* (2015)
	Ad libitum feeding of milk replacer	5	Schäff *et al.* (2016)
	Ad libitum feeding of milk replacer	8	Frieten *et al.* (2018)
	10 kg/day of whole milk	7	Haisan *et al.* (2018)
Elevated metabolic activity in the ruminal epithelium	2% of BW DM/day milk replacer with 28.5% CP and 15% crude fat	5	Naeem *et al.* (2014)
Elevated metabolic activity in the omental adipose tissue	1.26 MJ/kg BW$^{0.75}$ per day milk replacer with 28.5% CP and 15% crude fat	8	Leal *et al.* (2018)

Table 1 (*Continued*)

Item effect due to intensive feeding when compared to restricted milk feeding	Type of intensive milk or milk replacer feeding[2]	Duration in weeks	Reference
Feeding behaviour			
Elevated milk/milk replacer intake and less sign of hunger	*Ad libitum* feeding of milk powder	4	Hammon *et al.* (2002)
	Ad libitum feeding of whole milk	5	Jasper and Weary (2002)
	8 kg/day of milk and milk replacer/day[3]	7	Jensen and Holm (2003)
	Ad libitum feeding of whole milk	1	De Paula Vieira *et al.* (2008)
	Ad libitum feeding of milk replacer; 12 kg/day of whole milk	6	Borderas *et al.* (2009)[4]
		6	
	Ad libitum feeding of milk replacer	6	Miller-Cushon *et al.* (2013)
	Ad libitum feeding of milk replacer	5	Schäff *et al.* (2016)
	Ad libitum feeding of milk replacer	8	Gerbert *et al.* (2018)
Immune response and health			
Altered interferon-γ and *no* production of peripheral blood mononuclear cells *ex vivo*	2.5% of BW DM milk replacer with 30% CP and 20% crude fat	8.5	Nonnecke *et al.* (2003)
Greater plasma haptoglobin concentration 24 h after LPS challenge; greater neutrophil oxidative burst intensity after *Escherichia coli* co-culture	810 and 1180 g DM/day of milk replacer with 28% CP and 20% crude fat	6	Ballou (2012)
Faster improvement of faecal scores after infection with *Cryptosporidium parvum*	0.95 to 1.24 MJ/kg $BW^{0.75}$ per day milk replacer with 28% CP and 20% crude fat	3	Ollivett *et al.* (2012)
Decreased systemic inflammation after oral *Salmonella typhimurium* challenge in postweaning calves	610 and 735 g DM/day of milk replacer with 28% CP and 25% crude fat	6	Ballou *et al.* (2015)
Reduced plasma fibrinogen concentration in blood	*Ad libitum* feeding of milk replacer	5	Schäff *et al.* (2016)
Enhanced activation of pathways related to the intestinal immune system	*Ad libitum* feeding of milk replacer	8	Hammon *et al.* (2018)

[1]Intensive milk feeding is defined as daily milk or milk replacer intake of 20% of BW, *ad libitum* milk or milk replacer feeding or feeding enhanced amounts of milk replacer with elevated CP and fat content.
[2]When not stated in the table, milk replacer contained 21% to 23% of CP and 17% to 20% of crude fat based on DM. Whole milk contained 320 to 350 g CP and 370 to 400 g crude fat/kg milk.
[3]Data apply only for Holstein calves.
[4]Two studies in the reference.

and fat tissue as well as the ruminal epithelium (Naeem *et al.*, 2012 and 2014; Wang *et al.*, 2014; Leal *et al.*, 2018).

The improved growth development and protein accretion in calves fed intensively with milk or MR are confirmed by the stimulation of the somatotropic axis (Maccari *et al.*, 2015; Schäff *et al.*, 2016; Frieten *et al.*, 2018; Haisan *et al.*, 2018). Important elements of the somatotropic axis are growth hormone (**GH**), IGF-I and several IGF-binding proteins (**IGFBP**s). The postnatal interaction of GH, IGF-I and IGFBP affects body growth and organ development in mammals (Breier *et al.*, 2000), including the development of the mammary gland (Akers, 2006) and immune function (Clark, 1997). The stimulation of the postnatal somatotropic axis depends on the nutrient supply and reflects the glucose and insulin status of the animal (Brameld *et al.*, 1999; Renaville *et al.*, 2000; Smith *et al.*, 2002). Plasma IGF-I and IGFBP-3 concentrations are elevated, and the IGFBP-2 concentration is decreased during growth in well-nourished animals as compared to animals of same age with restricted feed intake (Breier *et al.*, 2000; Renaville *et al.*, 2000). A key factor in maturation of the somatotropic axis is the increased expression of the GH receptor, particularly in the liver, with age (Breier *et al.*, 2000; Hammon *et al.*, 2012). The GH receptor mediates GH action on IGF-I synthesis and secretion and is stimulated by insulin (Breier *et al.*, 2000; Butler *et al.*, 2003). The glucose, insulin, IGF-I and IGFBP-3 plasma concentrations are much greater, and hepatic gene expression of the GH receptor and IGF-I is higher in intensively milk-fed calves than in calves with restricted milk intake (e.g., 6 l MR/day; Maccari *et al.*, 2015; Schäff *et al.*, 2016; Frieten *et al.*, 2017 and 2018). The IGFBP-2 plasma concentration and hepatic gene expression behave the other way round, as expected from the literature (Renaville *et al.*, 2000; Schäff *et al.*, 2016; Frieten *et al.*, 2018). No signs of impaired insulin response are seen during enhanced milk feeding in calves (MacPherson *et al.*, 2019).

During the first weeks of life, the elevated concentrate intake in restrictively milk-fed calves cannot compensate for impaired nutrient intake due to reduced milk feeding, and consequently, the somatotropic axis is not stimulated during early postnatal life when concentrate and forage feeding are favoured instead of milk feeding. In particular, the elevated IGFBP-2 plasma concentration in milk-restricted-fed calves indicates an impaired nutrient intake (Renaville *et al.*, 2000; Schäff *et al.*, 2016; Frieten *et al.*, 2018). An impaired nutrient supply with decreased IGF-I and IGFBP-3 and increased IGFBP-2 plasma concentrations also occurs during weaning when milk feeding is reduced too quickly and the solid feed intake does not meet nutrition requirements (Schäff *et al.*, 2016; Frieten *et al.*, 2018). These changes in the somatotropic axis are reflected by a depressed growth rate during the weaning process (Schäff *et al.*, 2016; Frieten *et al.*, 2017). To prevent a growth depression during weaning in calves with an intensified milk-feeding programme, a delayed weaning age or individual weaning based on solid feed intake is recommended (Eckert *et al.*, 2015; de Passillé and Rushen, 2016; Welboren *et al.*, 2019).

Parameters of the somatotropic axis may provide useful information on the metabolic status and may help to avoid detrimental weaning programmes in calves.

Development and maturation of the gastrointestinal tract and immune response by intensive milk feeding

An intensive milk feeding strategy affects intestinal development. The size and the absorptive capacity increase in preweaning calves with an enhanced MR-feeding programme (Geiger *et al.*, 2016; Koch *et al.*, 2019). In addition, an intensive milk or MR-feeding programme seems to stimulate the expression of long non-coding RNA involved in the regulation of tight-junction protein synthesis (Weikard *et al.*, 2018). It is well established in ruminants that the diet affects tight-junction protein expression (Steele *et al.*, 2016). According to the upregulation of tight-junction protein-encoding genes, it is suggested that the first week of life is crucial for the development of the intestinal epithelium and the intestinal barrier of the mucosal immune system in calves (Malmuthuge and Guan, 2017). In piglets, specific amino acids can affect intestinal permeability and integrity, protein synthesis, intestinal repair after injury and cell proliferation in the gastrointestinal tract (Jacobi and Odle, 2012). Because of its composition and ingredients, milk provide the best conditions for nutrient supply in the postnatal and preweaning period to promote intestinal integrity in the bovine (Steele *et al.*, 2016).

There is growing evidence that an adequate nutrient supply is important for the maturation of the intestinal immune system and for successful defence against pathogens (Khan *et al.*, 2011; Hammon *et al.*, 2018). A greater nutrient supply may have beneficial effects on intestinal maturation, including the generation of a proper adaptive immune system and a stable microbiota, which may protect against diarrhoeal diseases in the neonatal and preweaning period. Common feeding schedules of not more than 6 kg of milk per day may delay the establishment of a proper immune response and microbiota in the intestine. Studies in neonatal calves have investigated the diet-dependent establishment of the intestinal microbiome, but the impact of the milk amount on the intestinal microbiome is still unclear (Malmuthuge and Guan, 2017). A higher plane (considering the amount of MR, concentration of MR and protein and fat concentration) of nutrition seems to protect the intestine against pathogenic infections and promote overcoming of pathogenic infections. Calves with a higher plane of nutrition (intake energy: 1.3 MJ/kg metabolic BW instead of 0.5 MJ/kg metabolic BW by MR feeding) indicate a faster resolution from diarrhoea caused by infection with *Cryptosporidium parvum* (Ollivett *et al.*, 2012). Ballou *et al.* (2015) showed that a higher plane of nutrition (610 and 735 g/day DM MR during week 1 and weeks 2 to 6, respectively, of a 28% CP and 25% fat MR instead of 409 g/day DM MR of a 20% CP and 20% fat MR) results in a higher resistance against *Salmonella typhimurium* in postweaning calves. Even there is first evidence that an intensive milk or MR feeding stimulates intestinal development and maturation and the intestinal immune

response (Hammon et al., 2018), more studies are needed to investigate the interaction between the changes of the intestinal microbiome and immune response due to an intensive milk-feeding programme.

An intensive milk feeding may delay rumen development by reducing solid feed intake during the early preweaning period (Baldwin et al., 2004; Khan et al., 2011 and 2016). However, solid feed intake and rumen development accelerate during the weaning process, and rumen function is not impaired at the end of the weaning process when calves received 20% instead of 10% of BW milk per day (Khan et al., 2011). Rumen papilla growth and concentrations of volatile fatty acids are the same when calves are fed MR ad libitum for 5 and 8 weeks after birth, respectively, compared to 6 kg/day MR intake (Schäff et al., 2018; Koch et al., 2019). These findings are supported by the fact that ad libitum milk-fed calves immediately increase their solid feed intake and plasma β-hydroxybutyrate concentration in blood when MR intake is reduced (Schäff et al., 2016; Frieten et al., 2017; Welboren et al., 2019). Plasma β-hydroxybutyrate results from ketogenesis from butyrate in the rumen epithelial cells and is an indicator for maturation of the rumen function (Baldwin et al., 2004). Interestingly, the metabolic activity in ruminal epithelium is enhanced in calves fed elevated amounts of MR (Naeem et al., 2012 and 2014).

In summary, an intensive milk-feeding regime is required to realise the potential for growth and development in preweaning calves. Body growth and organ maturation are improved with an intensive milk-feeding programme, and calves are less hungry and probably more resilient to infectious diseases during the preweaning period. The development of the forestomach could be delayed during the intensive milk-feeding period, but applying an adapted weaning protocol for intensive milk-fed calves avoids an impaired rumen development and body growth depression during the postweaning period.

Impact of preweaning growth and development on lifetime performance and health

Colostrum and milk feeding not only influence the postnatal and preweaning development and growth of the calves but also influence performance and health in later life (Van Amburgh und Soberon, 2013; Huber, 2018). The improved mammary gland development during the preweaning rearing period is an example of the importance of the nutrient supply during the preweaning period for organ development (Geiger et al., 2016; Soberon and Van Amburgh, 2017), with consequences for lifetime performance (Van Amburgh und Soberon, 2013). However, presently it is not known whether early calf nutrition has long-lasting effects on other organ systems, for example, the liver or the immune system. Culling rates are still high in dairy production, and metabolic diseases and immune suppression around calving are heavily involved in this unfavourable situation (Hare et al., 2006;

Ingvartsen and Moyes, 2015; Probo et al., 2018; Gross and Bruckmaier, 2019). Interestingly, different patterns of metabolic parameters due to variable milk or MR feeding in preweaning calves seem to be maintained when calves become dairy cows, and epigenetic effects due to different milk-feeding programmes during the preweaning period have been assumed (Kenéz et al., 2018). Postnatal nutritional programming is well known from human studies and in other species (Guilloteau et al., 2009b), but it still remains unclear whether variable metabolic profiles of young individuals are conserved and are the basis for the different metabolic types of the adults in their productive life span. Thus, more research is needed to investigate the impact of early calf nutrition on metabolic performance in later life and whether early calf nutrition may improve robustness and resilience in dairy cows.

Conclusions

An intensive milk-feeding programme, starting immediately after birth, with an enhanced colostrum intake and subsequent intensive milk feeding supports postnatal growth and development of dairy calves, prevents behavioural anomalies and promotes the raising of robust young animals. Providing only 4 to 6 kg milk/day to the preweaning calves is not consistent with animal welfare principles (FAWC, 2015; OIE, 2017; Huber, 2018). Thus, a change of the early calf management is needed to follow the natural processes of preweaning calf rearing, for example, as known from beef calf management (Egli and Blum, 1998; Schiessler et al., 2002). Research will continue to investigate the impact of an intensive milk-feeding regime on raising robust and well-performing dairy cows and bulls.

Declaration of interest
The authors declare no conflicts of interest.

Ethics statement
None.

Software and data repository resources
None.

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