Rethinking Colostrum: It's More than Just Immunoglobulins

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▪ Take Home Messages

- The pre-weaning period is a period of life where the calf is undergoing significant developmental changes and this development is directly linked to future productivity in the first and subsequent lactations.
- Pre-weaning growth rate and primarily protein accretion appears to be a key factor in signaling/communicating with the tissues that enhances lifetime milk yield.
- Anything that detracts from feed intake and subsequent pre-weaning growth rate reduces the opportunity for enhanced milk yield as an adult.
- Nutrient supply, both energy and protein, are important and protein quality and digestibility are essential.
- There are no substitutes for liquid feed prior to weaning that will enhance the effect on long-term productivity.
- Factors other than immunoglobulins in colostrum modify feed intake, feed efficiency and growth of calves and can enhance the effect of early life nutrient status.
- As an industry and as nutritionists we need to talk about metabolizable energy, protein intake and status relative to maintenance, and stop talking about cups, quarts, gallons, buckets and bottles of dry matter, milk, milk replacer, etc. The calf has discrete nutrient requirements not related to dry matter and liquid volume measurements.
- The effect of nurture is many times greater than nature and the pre-weaning period is a phase of development where the productivity of the calf can be modified to enhance the animal's genetic potential.
- Adhering to specific growth targets throughout the rearing period and calving as early as feasible is essential to ensure optimum economic returns in the first lactation within the management system.

▪ Lactocrine Hypothesis: Colostrum's role

It has been well recognized that the phenotypic expression of an individual is affected by both genetic ability and the environment. To some degree, while in the uterus, the mother controls the environment in which the fetus is developing, influencing in this way the expression of the genetic material. There is good evidence that this environment can play a role in long-term productivity in beef cattle (Summers and Funston, 2012). For example, heat stress of the dam during late fetal development has been shown to affect subsequent growth, immune function and feed efficiency in the calf (Tao et al., 2012), and subsequent milk production (Monteiro et al., 2016). In that study calves from heat stressed dams had lower circulating IgG's, lower efficiency of absorption, reduced immune cell proliferation and lower growth rate through weaning, indicating that the effect of heat stress on the calf carried over through at least the weaning period. Thus, environmental factors affect the calf during fetal development and the productivity of the calf can be modified – an outcome that has not been fully recognized and appreciated through the pre-weaning period. Once the calf is born, it will carry these effects with it into post-natal life, where other environmental and maternal factors will continue to impact the productivity of the animal. The first mammary secretion, colostrum, plays an important role in the development of the calf and although traditionally considered only for its role in immune system function, data generated over many years suggests that its role in immune system function is more complex than immunoglobulins.

▪ It's Not Just IgG's - Role of Maternal Leukocytes

Colostrum is rich in many different cell types, many of which are lumped into the term "somatic cells," analyzed as such and not always considered positively. However, those cells are important and data generated in other species clearly demonstrated the presence and "trafficking" of cells, primarily leukocytes, into circulation of the neonate (Williams, 1993; Sheldrake and Husband, 1985). More recently, work has been conducted to understand if the uptake of the maternal leukocytes into circulation has any impact on the function and capacity of the immune system of the calf. The implication is that leukocytes from the dam will carry "maternal memory" from prior exposure and recognition of pathogenic organisms, which if functional, can enhance cellular immunity in the calf. This adds a new dimension to the role of colostrum with respect to immunity and impacts colostrum management if the presence and availability of these cells is important for full immune system stimulation and function in the calf.

Papers have been published over the last decade that clearly demonstrate the uptake of leukocytes from colostrum into the circulation of the calf (Reber et al, 2006; 2008ab; Donovan et al. 2007; Langel et al., 2015; Novo et al., 2017). The data from Reber et al. (2006) clearly demonstrated that maternal leukocytes were transferred into the calf within 12 to 24 hr of colostrum ingestion and disappeared from circulation within 36 hr after ingestion. The implication of this data was that maternal leukocytes from the blood stream of the dam were modified in the mammary gland to be more functional and capable of being absorbed into circulation in the calf. This is significant because it implies an active process and not just a process that passively accepts whatever cell might be present in the colostrum. Follow-up work from Reber et al. (2008ab) further demonstrated that the maternal leukocytes were absorbed into circulation and those cells enhanced the rate of maturation of immune cells in the calf, as well as the ability of the cells to recognize particular antigens. The majority of these developmental changes occurred within the first two weeks post colostrum ingestion.

Following this concept, Donovan et al. (2007) studied the effect of maternal leukocyte uptake on cellular immunity in the calf by targeting specific antigen responses. In this study, they vaccinated the dams against BVDV using an inactive vaccine, but did not vaccinate them for mycobacterial antigens, thus the cells would be naïve to the mycobacteria. The colostrum was then fed intact, after freezing or after cell-removal. Calves were then challenged with BVDV antigens. Calves fed the intact colostrum had enhanced immune responsiveness whereas calves fed the frozen and cell free colostrum did not respond similarly. All calves had similar responses to the mycobacterium antigens demonstrating the lack of maternal information transfer. This study suggests freezing colostrum negatively affects the population of maternal leukocytes, preventing them from being absorbed. It further begs the question about the significance of this outcome given our management of colostrum to ensure low bacteria counts and disease transmission through freezing and pasteurizing.

The positive effect of cell transfer from colostrum on cellular immunity was further demonstrated in both Holstein and Jersey calves in work from Langel et al. (2015) and Novo et al. (2017). In the study from Langel et al. (2015) calves were fed 4 qt of either whole colostrum or cell-free colostrum at birth. Calves receiving the cell-free colostrum had higher respiratory scores at 38 d of age and there were no differences in fecal consistency. Calves fed the whole colostrum had immune cells with the ability to recognize particular pathogens and the only manner in which this could occur would be through the exchange of information from the maternal cells to the intrinsic leukocytes in the calf. In the study of Novo et al. (2017) calves were fed whole fresh colostrum or frozen colostrum in each case from their own dams. Calves given the frozen colostrum had more diarrhea on day 7 than calves fed fresh colostrum. In addition, the calves fed frozen colostrum had less red blood cells, less hemoglobin and more anemia from 21 to 28 days. Overall, the number of leukocytes remained constant in the calves fed whole colostrum whereas the lymphocyte population increased in the calves fed frozen colostrum after 7 days of age. Taken together, these studies demonstrate changes in cellular immunity in neonatal calves with modifications to their ability to recognize possible pathogens and challenges to the system. Implications for colostrum management are that fresh colostrum is best for ensuring the transfer of this information from the dam to the offspring, whether freezing or pasteurizing, but the degree to which this lack of leukocyte transfer would affect the long-term immune function of the animal is still unknown. Thus, it is more prudent to maintain our current protocols and freeze and or pasteurize colostrum to ensure pathogens are managed and colostrum quality is maintained.

■ Colostrum as a Communication Vehicle

The effect and extent of maternal influence in the offspring's development does not end at parturition, but continues throughout the first weeks of life through the effect of milk-born factors, including colostrum, which have an impact on the physiological development of tissues and functions. A concept termed the "lactocrine hypothesis" has been introduced and describes the effect of milk-borne factors on the epigenetic development of specific tissues or physiological functions in mammals (Bartol et al., 2008). Data relating to this topic has been described in neonatal pigs (Donovan and Odle, 1994; Burrin et al., 1997) and calves (Baumrucker and Blum, 1993; Blum and Hammon, 2000; Hammon et al., 2012). The implication of this hypothesis and the related observations are that the neonate can be programmed maternally and postnatally to alter development of a particular process and potentially modify the genetic ability of the animal.

At birth, the gastrointestinal tract (GIT) is highly developed but naïve and will undergo significant growth, specifically protein synthesis, cell growth and enzyme production, to enhance digestion, absorption and create a more robust barrier for immune system defense. Colostrum contains many growth factors that are active at enhancing the development of the GIT (Table 1) – an area that has been extensively researched and reviewed (Odle et al., 1996; Blum and Hammon, 2000; Steinhoff-Wagner et al. 2011; Hammon et al. 2012). For example, colostrum feeding has been shown to positively affect the development of the gastrointestinal tract (GIT) and enhance energy metabolism of the calf. Adequate intake of these non-nutritive factors appears to be important for establishing gastrointestinal development for enhanced nutrient intake and nutrient utilization (Blum and Hammon, 2000; Hammon et al. 2012).

Table 1. Nutrients, energy, immunoglobulins, hormones and growth factors in colostrum and milk.

Components	Units	Colostrum	Mature Milk
Gross Energy	MJ/L	6	2.8
Crude protein	%	14.0	3.0
Fat	%	6.7	3.8
Immunoglobulin G	g/L	81	<2
Lactoferrin	g/L	1.84	Undetectable
Insulin	µg/L	65	1
Glucagon	µg/L	0.16	0.001
Prolactin	µg/dL	280	15
Growth hormone	µg/dL	1.4	<1
IGF-1	µg/dL	310	<1
Leptin	µg/dL	30	4.4
TGF-α	µg/dL	210	<1
Cortisol	ng/ml	11.2	1.2
17βEstradiol	µg/dL	3.3-4.7	0.54

Several studies have identified factors in colostrum that enhance crypt cell growth and development, which in turn enhances villus height in calves (Blum and Hammon, 2000; Blätter et al., 2001; Roffler et al., 2003). In addition to the increase in absorption capacity through increased surface area, there is a concomitant increase in enzyme production, especially lactase that enhances digestion and absorption of glucose (Hammon and Blum, 1997; Steinhoff et al., 2010). This leads to data like that from Steinhoff-Wagner et al. (2011) where they clearly demonstrated that colostrum feeding compared to iso-nutrient levels of a milk-based formula enhanced the glucose uptake of calves fed solely colostrum for up to four days of life. In that experiment, first milking colostrum was fed as the first meal and second, third and fourth milking colostrum was fed over the next three days, respectively, to examine differences in dietary glucose uptake, insulin responsiveness and endogenous glucose production. Calves fed colostrum had higher levels of plasma glucose, similar endogenous glucose production and higher plasma insulin concentrations post feeding. This suggests that colostrum enhanced the absorption of glucose, and the insulin in the colostrum was absorbed by the GIT, which contributed to the endogenous insulin production. It is also important to note that glycogen reserves were greater in the calves fed colostrum and that serum urea nitrogen was lower and amino acid concentration was greater, implying a more anabolic state with colostrum intake as compared to similar nutrient intake from formula. Thus, it appears that in addition to the Ig's, the other non-nutritive factors in colostrum are important to establish enhanced energy utilization and GIT development in newborn calves. These potential effects should be considered when evaluating and diagnosing differences in calf performance under similar management and nutritional conditions.

Given the data on development of the GIT, the next logical outcome is to look for growth responses based on the amount of colostrum fed in the first few hours of life or to find comparison where alternatives to the dam's colostrum were fed and evaluate differences. For example, Jones et al. (2004) examined the differences between maternal colostrum and a serum-derived colostrum replacement. In that study, two sets of calves were fed either maternal colostrum or serum-derived colostrum replacement with nutritional components balanced. The colostrum replacer was developed to provide adequate immunoglobulins to the neonatal calf, however the other non-nutritive factors found in colostrum were not considered. The results demonstrated that in the first 7 days of life, the calves fed maternal colostrum had significantly higher feed efficiency; the difference established in that period was still apparent at 29 days compared to calves fed serum-derived colostrum replacement. It is important to recognize the IgG status of calves on both treatments were nearly identical suggesting that factors in colostrum other than IgG's were important in contributing to the differences. Further, data from Faber et al. (2005) demonstrated that the amount of colostrum, 2 L or 4 L, provided to calves at birth significantly increased pre-pubertal growth rate under similar nutritional and management conditions, as well as tendencies for greater herd life and milk yield through two lactations.

To extend and try to better understand this data, Soberon and Van Amburgh (2011) examined the effect of colostrum status on pre-weaning ADG and also examined the effects of varying milk replacer intake after colostrum ingestion (Table 2). Calves were fed either high levels (4 L) or low levels (2 L) of colostrum, and then calves from these two groups were subdivided into two groups that were fed milk-replacer in limited amounts or ad-libitum. Calves fed 4 L of colostrum had significantly greater average daily gains pre-weaning and post-weaning and greater post-weaning feed intake, consistent with the data from Faber et al. (2005) and Jones et al. (2004). The observations from these experiments reinforce the need to ensure that calves receive as much colostrum as possible over the first 24 hr and possibly over the first 4 days, as described by Steinhoff-Wagner et al. (2011), to ensure greater nutrient availability and absorption for the calf. The non-nutritive factors in colostrum other than Ig's appear to be important for helping the calf establish a stronger anabolic state and develop a more functional GIT barrier and surface area for absorption.

Table 2. Effect of high (4+2 L) or low (2L) colostrum and ad-lib (H) or restricted (L) milk replacer intake on feed efficiency and feed intake in pre and post-weaned calves (Soberon and Van Amburgh, 2011).

Treatment[1]	***HH***	***HL***	***LH***	***LL***	*Std dev*
N	34	38	26	27	
Birth wt, kg	44.0	43.4	41.8	43.3	0.95
Birth hip height, cm	80.5	80.3	80.0	80.9	0.56
IgG concentration, mg/dl*	2,746[a]	2,480[b]	1,466[c]	1,417[c]	98
Weaning wt, kg	78.2[a]	63.5[b]	72.2[c]	62.4[b]	1.89
Weaning hip height, cm	93.0[a]	88.6[b]	91.5[a]	89.6[b]	0.60
ADG pre-weaning, kg	0.79[a]	0.42[b]	0.67[c]	0.39[b]	0.028
Hip height gain, pre-weaning, cm/d	0.248[a]	0.158[b]	0.227[a]	0.161[b]	0.009
ADG birth to 80 d, kg	0.78[a]	0.59[bc]	0.66[b]	0.53[c]	0.034
Hip height gain, birth to 80 d, cm/d	0.214[a]	0.157[b]	0.184[c]	0.148[b]	0.008
Total milk replacer intake, kg DM	44.4[a]	20.5[b]	40.9[c]	20.0[b]	1.2
Grain intake pre-weaning, kg	2.5[a]	12.0[b]	2.1[a]	9.7[b]	1.5
ADG/DMI, pre-weaning	0.60	0.61	0.67	0.61	0.042
ADG post-weaning, kg	1.10[a]	0.97[ab]	0.88[b]	0.92[b]	0.061
DMI post-weaning, kg/d	2.89[ab]	2.89[a]	2.58[c]	2.66[bc]	0.104
ADG/DMI post-weaning	0.359	0.345	0.335	0.358	0.020

[1]HH = high colostrum, high feeding level, HL = High colostrum, low feeding level, LH = Low colostrum, high feeding level, LL = Low colostrum, low feeding level. Rows with different superscripts differ $P < 0.05$.

Also, colostrum is the first meal and accordingly is very important in establishing the nutrient supply needed to maintain the calf over the first day of life. The amount of colostrum has always focused on the idea that we are delivering a specific amount of immunoglobulins (Ig's) to the calf, and many times we underestimate the nutrient contribution of colostrum. Further, many times of year, we tend to underestimate the nutrient requirements of the calf, especially for maintenance. For example, a newborn Holstein calf at 38 kg birth weight has a maintenance requirement of approximately 1.55 Mcals ME at 22 °C. Colostrum contains approximately 2.51 Mcals metabolizable energy

(ME)/lb, and a standard feeding rate of 2 L of colostrum from a bottle contains about 1.5 Mcals ME. Thus, at thermoneutral conditions, the calf is fed just at or slightly below maintenance requirements at its first feeding. For comparison, if the ambient temperature is 0 °C the ME requirement for maintenance is 2.4 Mcals, which can only be met if the calf is fed approximately 0.45 kg of DM or about 3.3 L of colostrum. This simple example illustrates one of the recurring issues with diagnosing growth and health problems in calves – the use of volume measurements to describe nutrient supply instead of discussing energy and nutrient values. Two liters of colostrum sounds good because that is what the bottle might hold, but it has little to do with the nutrient requirements of the calf.

Managing the calf for greater intake over the first 24 hours of life is important if we want to ensure positive energy balance and provide adequate Ig's and other components from colostrum for proper development. For the first day, at least 3 Mcals ME (approximately 4 L of colostrum) would be necessary to meet the maintenance requirements and also provide some nutrients for growth. On many dairies this is done via an esophageal feeder and the amount is dictated by the desire to get adequate passive transfer. Those dairies not tube feeding should be encouraging up to 4 L by 10 to 12 hours of life to ensure that colostrum fed not only meets the Ig needs of the calf, but also ensures that the nutrient requirements are met for the first day of life.

▪ Nutrient Status

There are several published studies and studies in progress that have both directly and indirectly allowed us to evaluate milk yield from cattle that were allowed more nutrients up to eight weeks of age (Table 2). The earliest of these studies investigated the effect of suckling versus controlled intakes or ad-libitum feeding of calves from birth to 42 or 56 days of life (Foldager and Krohn, 1994; Bar-Peled et al, 1997; Foldager et al, 1997). In each of these studies, increased nutrient intake prior to 56 days of life resulted in increased milk yield during the first lactation, which ranged from 450 to 1,361 additional kilograms (Table 3). Although they are suckling studies, milk is most likely not the factor of interest, but nutrient intake in general – a fact that is demonstrated in the more recent data.

A meta-analysis was conducted to evaluate the data presented in Table 3 using Comprehensive Meta-Analysis software (CMA, v2.2.064, Biostat, Englewood, NJ; Borenstein et al., 2005). In the first analysis, the treatment calves, or those calves that received more nutrients from milk or milk replacer prior to weaning, were estimated to produce 429 ± 106 kg more milk in first lactation ($P < 0.001$) compared to control calves. This analysis did not include ADG or any other predictors and was simply an evaluation of treatment effect. It should be immediately recognized that within these data sets, starter intake was not well described and any starter intake or additional nutrient intake would enhance the outcome; this, however, is difficult to quantify. In the paper by Soberon et al. (2012), the role of starter intake was discussed and based on recent studies investigating starter intake and growth rates, it would be very difficult for calves to achieve the nutrient intakes and associated growth rates in the first 4 to 6 wk of life necessary to realize the milk yield outcome identified in this analysis. Equally important was the odds ratio from this analysis of 2.09 ($P = 0.001$) which indicated that a calf receiving more nutrients during the pre-weaning period was two times more likely to produce more milk than a calf that is restricted during the same period.

Table 3. Milk production differences as adults among treatments where calves were allowed to consume approximately 50% more nutrients than the standard feeding rate prior to weaning from either milk or milk replacer.

Study	Milk response (kg)
Foldager and Krohn, 1994	$1,405^{s}$
Bar-Peled et al., 1997	453^{t}
Foldager et al., 1997	519^{t}
Ballard et al., 2005 (@ 200 DIM)	700^{s}
Shamay et al., 2005	981^{s}
Drackley et al., 2007	835^{s}
Raeth-Knight et al., 2009	718^{ns}
Terre et al., 2009	624^{ns}
Morrison et al., 2009	0^{ns}
Moallem et al., 2010	732^{s}
Davis-Rincker et al., 2011	416^{ns}
Soberon et al., 2012	552^{s}
Margerison et al., 2013	595^{s}
Kinzelback et al., 2015	0^{ns}

Milk response is the difference between treatment milk yield minus control. ^{s} $P < 0.05$, ^{t} $P < 0.1$, ^{ns} $P > 0.1$

Each study offered different quantities and qualities of nutrients to treatment groups, thus to help evaluate the outcome of milk yield, ADG was included in the analysis to account for the effect of nutrient intake and nutrient quality. In order to evaluate the effect of ADG on first lactation milk yield, ADG was included in the analyses as a predictor variable and analyzed by meta-regression. In that analyses, a prediction equation was generated where first lactation milk yield = -106 kg + 1,551.4 (± 637) kg*ADG (Low limit 301 kg, upper limit 2,801 kg; Z value 2.41; $P = 0.01$), where ADG is kg pre-weaning average daily gain. This means that for every kg of pre-weaning ADG, calves produced 1,551 kg more milk during their first lactation (Soberon and Van Amburgh, 2013). This was a higher but consistent response to what was observed among two herds of 850 kg and 1,113 kg per kg of ADG (Soberon et al., 2012) indicating that the response to pre-weaning nutrient intake is not constant among herd and most likely varies with the management and environment of the herd, along with the herd's genetic potential for milk yield.

▪ Summary

Colostrum is an important part of early calf development, from immune function to digestion and metabolism. The constituents of colostrum are there to ensure the calf is provided support that enables success at the beginning of extra-uterine life. Given the data on the effects of colostrum on metabolism, growth and development of the calf, a management suggestion would be to feed first milking colostrum to the calf immediately, then feed colostrum from milkings 2 through 4 (day one and two of lactation) to the calves over the first 4 days. This would ensure the non-nutritive factors are supplied to the calf during the period the calf is responsive to them in an effort to enhance intestinal development and function, along with enhancing glucose absorption during a period when energy status is extremely important. Our management approaches and systems need to recognize these effects and capitalize on them. Improving the nutrition and management of calves appears to improve the sustainability of the animal through increased productivity throughout life. This has implications for animal welfare, the environment and profitability. We have much to learn about the consistency of the response and the mechanisms that are being affected.

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