

Ruminant Session

Early Life Nutrition and Management Impacts Long-Term Productivity of Calves

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Lactocrine Hypothesis

The concept of a "lactocrine hypothesis" has been recently introduced and describes the effect of milk-born factors, including colostrum in this definition, on the epigenetic development of specific tissues or physiological functions (Bartol et al., 2008). Conceptually this topic is not new but the terminology is useful and the ability of several groups to make a direct connection from a milk-born factor to a developmental function at the tissue or behavior level is significant (Nusser and Frawley, 1997; Hinde and Capitanio, 2010). Data relating to this topic has been described and discussed by others in neonatal pigs (Donovan and Odle, 1994; Burrin et al., 1997) and calves (Baumrucker and Blum, 1993; Blum and Hammon, 2000; Rauprich et al. 2000). The implication of this hypothesis and these observations are that the neonate can be programmed maternally and post-natally to alter development of a particular process. It is not well understood if the lactation response is a function of total nutrient intake or if there are factors in whole milk that are responsible for the developmental function. In primates, Hinde and Capitanio (2010) were able to demonstrate that maternal milk composition and yield impacted offspring behavior, which has implications for the dairy industry and early life human health and development.

In calves the effects of suckling, controlled intakes and *ad-libitum* feeding of calves from birth up to 56 days of life have found that increasing the nutrient intake prior to 56 days of life from milk resulted in increased milk yield during first lactation ranging from 450 to 1,300 kg compared to the milk yield of restricted fed calves during the same period (Foldager and Krohn, 1994; Bar-Peled et al, 1997; Shamay et al., 2005; Terré et al., 2009; Moallem et al. 2010; Soberon et al., 2012). In Moallem et al., (2010), the effects of pre-weaning nutrition on long term productivity were associated with the type and quality of nutrients fed. Moallem et al. (2010) observed significantly (10.3%) higher milk yields during first lactation from heifers fed whole milk *ad-libitum* compared to heifers fed milk replacer *ad-libitum* during the same period and suggested that milk replacer did not contain the same biologically active factors as milk and thus did not impart any lactocrine effects on the calves. However, the data of Soberon et al. (2012) and others suggest that the long-term effect is related to nutrient intake and pre-weaning growth rates and not some milk-born factor. A review of the studies conducted to date would suggest that the long-term milk response is related to protein synthesis, thus energy intake above maintenance coupled with adequate protein and amino acids are essential for the signaling mechanism important for long-term changes in productivity. Any signals from colostrum would only enhance this observation.

Colostrum's role

Colostrum is known to be rich in a variety of molecules (ratio of colostrum composition to mature milk composition), including relaxin (>19:1 pig), prolactin (18:1 cow), insulin (65:1 cow), IGF-1 (155:1 cow), IGF-2 (7:1 cow), and leptin (90:1 humans) (Odle et al., 1996; Blum and Hammon, 2000; Wolinski et al., 2005; Bartol et al., 2008).

Colostrum is well known to have major effects on the development of the gastrointestinal tract for a long period of time, but the exact mechanisms are still not well understood. During the first few days

of life in neonatal piglets, a notable increase in the length, mass, DNA content, and enzymatic activities of certain enzymes (lactase) occur in the small intestine for neonates fed colostrum/milk versus a control of water (Widdowson et al. 1976, Burrin et al., 1994). This was originally thought to be mediated by differences in nutrient intake between milk and water (Burrin et al. 1992), however other studies have demonstrated differences between animals fed colostrum, rich in growth factors, versus milk with comparable energy values (Burrin et al., 1995). Although there are studies that don't agree with Burrin et al., (1995) and continue to promote nutrient intake as the driving factor (Ulshen et al., 1991), there is potential for non-nutrient factors to play a major role in the development of the gastrointestinal tract.

Further, Burrin et al. (1995) examined the effects of feeding colostrum, mature milk, formula (similar macronutrient composition to colostrum), and water on circulating metabolites and protein synthesis in piglets. The most significant finding was that the increased rate of protein synthesis in skeletal and jejunal protein synthesis of colostrum fed calves versus the other groups, although blood metabolite concentrations, including insulin, were not different. This is significant because it suggests other factors other than nutrient intake induced gastrointestinal and protein synthesis changes in the neonatal piglet. The group speculated that the reason for increased protein synthesis, regardless of treatment, was due to high circulating insulin levels postprandial during the first 6 hours, and then the protein synthesis was sustained by increased IGF-1 concentrations from 6-24 hours post-prandial resulting in treatment differences.

Bartol et al. (2008) demonstrated that neonatal piglets provided sows milk during the first 3 days of life had better reproductive performance later in life because of high levels of milk-borne relaxin concentrations. It was identified that there are relaxin receptors present at birth in uterine and cervical tissues, and the binding of these receptors by factors in colostrum induces estrogen receptor differentiation and proliferation through intermediates found in the stroma, called relaxomedans. After day 3, estrogen-mediated events are the basis for uterine and cervical development, and the excessive proliferation of estrogen-receptors induced by relaxin ensures that critical estrogen events are recognized and optimized and proper reproductive tissue changes are induced. The highest relaxin concentrations are found in a sow's milk 24-48 hr after birth, correlating with production of colostrum. Detectable relaxin concentrations of 200 pg/mL are found in piglet blood plasma whereas relaxin concentrations are undetectable in piglets fed milk replacer. In addition, piglets that received relaxin versus piglets deprived of relaxin resulted in significant reproductive outcomes.

Work from Faber et al. (2005) in calves demonstrated that the amount of colostrum provided to calves at birth significantly influence pre-pubertal growth rate and showed a trend for milk yield through the second lactation. Further, Jones et al. (2004) examined the differences between maternal colostrum and 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. Serum-derived colostrum replacer was developed to provide essential immunoglobulins to a neonatal calf, however the colostrum replacer does not generally contain the other bioactive factors that colostrum contains. These two groups were then further separated into calves fed milk-replacer with or without animal plasma, yielding four different groups. The results demonstrated that calves fed maternal colostrum had significantly higher feed efficiency compared to calves fed serum-derived colostrum replacement. The IgG status of the calves on both treatments were nearly identical suggesting that other factors in colostrum other than IgG's were important in contributing to the differences. Soberon and Van Amburgh (2011) continued to examine the effect of colostrum status on pre-weaning ADG and also examined the effects of varying milk replacer intake after colostrum ingestion. Calves were fed either high levels (4 liters) or low levels (2 liters) of colostrum, and then calves from these two groups were subdivided into two more groups being fed milk-replacer at limited amounts or ad-libitum. Comparing calves fed 4 liter of colostrum and ab libitum intake of milk replacer versus 2 liter of colostrum and ab libitum of milk replacer, calves fed 4 liters of

colostrum had significantly higher average daily gains pre-weaning and post-weaning. Therefore, it can be logically concluded that if colostrum induces changes in feed efficiency, than the first feeding can possibly affect future milk production.

Finally, Steinhoff-Wagner et al. (2010) examined the effects colostrum has on the ability of neonates to regulate glucose, through both exogenous absorption and endogenous production. The results of this study demonstrated that calves fed colostrum had significantly higher plasma circulating glucose levels in comparison to formula fed calves, however the gluconeogenic ability did not differ between the two groups. This suggests that in colostrum-fed calves glucose absorption capacity are increased in comparison to milk-replacer fed calves, as mentioned above. These results were verified by significantly higher postprandial glucose concentrations, and ensuing higher insulin concentrations, in colostrum fed versus milk replacer fed calves. During post-prandial periods, colostrum-fed calves had higher liver glycogen concentrations and g6pase activities, indicating better glucose and galactose hepatic absorption. This has implications for lactose digestion and absorption. First pass uptake of [U-¹³C]-glucose, or the glucose utilization in splanchnic tissue (intestine and liver), was lower in colostrum fed calves than milk replacer fed calves. This indicates that glucose was either less absorbed or more utilized in splanchnic tissue in formula-fed calves, resulting in lower percentage use in colostrum-fed calves. Additionally, [U-¹³C]-glucose concentration was significantly higher in calves fed colostrum over milk-replacer, similar to the xylose absorption data presented earlier. Again, this supports the idea that glucose absorption is enhanced in colostrum-fed calves versus milk-replacer fed calves. Finally, plasma glucose concentrations were significantly higher in calves fed colostrum during feed deprivation of 15 hours and plasma urea concentrations were significantly higher in formula-fed calves. This suggests that calves fed colostrum had higher glycogen concentrations and did not utilize protein catabolism. If the glucose uptake differences were to persist, it would help us understand the role of factors in colostrum other than Ig's important for long-term productivity.

Nutrient status and long-term productivity

There are several studies in various animal species that demonstrate early life nutrient status has long-term developmental effects. Aside from the improvement in potential immune competency, there appear to be other factors that are impacted by early 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. The earliest of these studies investigated either 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 that ranged from 1,000 to 3,000 additional pounds compared to more restricted fed calves during the same period (Table 1). Although they are suckling studies, milk is most likely not the factor of interest, but nutrient intake in general and this is demonstrated in the more recent data.

In the study conducted at Miner Institute, Ballard et al. (2005), reported that at 200 days in milk, the calves fed milk replacer at approximately twice normal feeding rates produced 1,543 pounds milk more than the calves that received one pound of milk replacer powder per day. Calving age in that study was not affected by treatment. Overall, averaging the studies, there is a 1,500 pound response to increasing nutrient intake prior to weaning for first lactation milk yield. The significant observation is that the effect of intake level needs to be accomplished through liquid feed intake.

The responses in the studies of Shamay et al. (2005) and Moallem et al. (2010) are significant, specifically because they suggest that milk replacer quality is important to achieve the milk response, as is protein status of the animal post weaning. In that study, the calves were fed a 23%

CP, 12% fat milk replacer containing some soy protein or whole milk. Further, post-weaning the calves were fed similarly until 150 days of gain, and the diets were protein deficient (~13.5% CP). Starting at 150 days calves from both pre-weaning treatments were supplemented with 2% fish meal from 150 to 300 days of life. The calves allowed to consume the whole milk (ad libitum for 60 minutes) and supplemented with the additional protein produced approximately 1,700 pounds more milk in the first lactation indicating that the early life response could be muted by inadequate protein intake post-weaning.

Table 1. Milk production differences among treatments where calves were allowed to consume approximately 50% more nutrients than the standard feeding rate prior to weaning from liquid feed.

Study	Milk yield, lb
Foldager and Krohn, 1991	3,092
Bar-Peled et al., 1998	998
Foldager et al., 1997	1,143
Ballard et al., 2005 (@ 200 DIM)	1,543
Shamay et al., 2005 (post-weaning protein)	2,162
Rincker et al., 2006 (proj. 305@ 150 DIM)	1,100
Drackley et al., 2007	1,841
Raeth-Knight et al., 2009	1,582
Terre et al., 2009	1,375
Morrison et al., 2009 (no diff. calf growth)	0
Moallem et al., 2010	1,600
Soberon et al., 2011	1,217

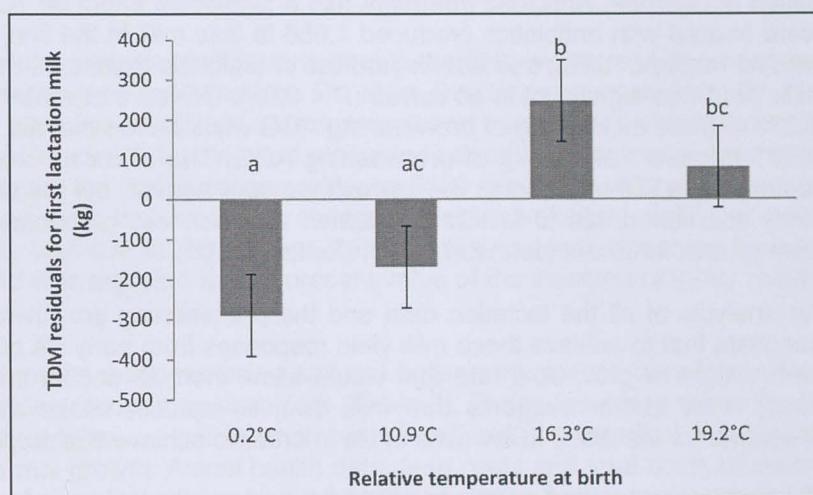
Finally the data of Drackley et al. (2007) again demonstrate a positive response of early life nutrition on first lactation milk yield. In this study, calves were fed either a conventional milk replacer (22:20; i.e. 22% protein, 20% fat) at 1.25% of the body weight (BW) or a 28:20 milk replacer fed at 2% of the BW for week one of treatment and then 2.5% of the BW from week 2 to 5 and then systematically weaned by dropping the milk replacer intake to 1.25% of the BW for 6 days and then no milk replacer. All calves were weaned by 7 weeks of age and after weaning all calves were managed as a single group and bred according to observed heats. The heifers calved between 24 and 26 months of age with no significant difference among treatments. Calving BW were also not different and averaged 1,278 lb. Milk yield on average was 1,841 pounds greater for calves fed the higher level of milk replacer prior to weaning.

The Cornell University Dairy Herd started feeding for greater pre-weaning BW gains many years ago and we have over 1,200 weaning weights and 3+ lactations with which to make evaluations outside of our ongoing study. What makes our approach to this unique is the application of a Test Day Model (TDM) (Everett and Schmitz. 1994; Van Amburgh et al., 1997) for the analyses of the data. This approach allows us to statistically control for factors not associated with the variables of interest and is the same approach that has been used to conduct sire summaries and daughter evaluations and develop heritabilities for genetic traits. Thus, the outcome is mathematically more robust and allows us to look within a herd over time with less bias and to look at herd responses independent of formal treatments. The resulting residuals are standardized which makes them additive over the life of the animal and they can be calculated for individual test days or over the lactation. The power of this type of analyses is much more significant compared to comparing daily milk or even ME305 milk and helps us partition out variance not associated with the variables of interest.

We analyzed the lactation data of the 1,244 heifers with completed lactations using the TDM approach and statistically analyzed several factors related to early life performance and the TDM

milk yield residuals (Soberon et al., 2012). The factors analyzed were birth weight, weaning weight, height at weaning, BW at 4 weeks of age and several other related and farm measurable factors. From a management perspective the most interesting observation was the relationship among two factors, growth rate prior to weaning and intake over maintenance and first lactation milk yield. In these analyses, the strongest relationship associated with first lactation milk production was growth rate prior to weaning and the findings are consistent with the data presented in Table 1. In our data set, for every 1 pound of average daily gain (ADG) prior to weaning (or at least 42 to 56 days of age), the heifers produced approximately 937 pounds more milk ($P < 0.01$) (Table 2). The range in pre-weaning growth rates among the 1,244 animals were 0.52 to 2.76 pounds per day and the range was actually quite puzzling to us. Our feeding program at the research farm is straightforward: 1.5% BW dry matter from day 2 to 7 and then 2% of BW dry matter from day 8 to 42 of a 28:15 or 28:20 milk replacer mixed at 15% solids. Free choice water is offered year around and starter is offered from day 8 onward. At that feeding rate, we are offering twice the industry standard amount and had assumed it was enough for overcoming the maintenance requirement and provide adequate nutrients for growth, even in the winter. However, when we analyzed the TDM residuals by temperature at birth, a very significant observation was made (Figure 1).

Figure 1. Test Day Model residuals in kg of milk, averaged by temperature at time of birth with mean temperature in Celsius. Columns with different superscripts differ ($P < 0.05$).



These data suggest that although we are meeting the maintenance requirements of the calves from a strict requirement calculation, we are not providing enough nutrients above maintenance to optimize first lactation milk production. We need to remember that the thermoneutral zone for calves is 68° to 82° F and that when the temperature drops below that level, intake energy will be used to generate heat instead of growth. In addition, when we analyzed the data by lactation, the response increased as the animals matured (Table 2).

Table 2. Predicted differences by TDM residual milk (lb) for 1st, 2nd, and 3rd lactation as well as cumulative milk from 1st through 3rd lactation as a function of pre-weaning average daily gain and energy intake over predicted maintenance for the Cornell herd.

Lactation	n	Predicted difference in milk per lb of pre-weaning ADG		Predicted difference in milk (lb) for each additional Mcal intake energy above maintenance	
			P value		P value
1 st	1244	850	< 0.01	519	< 0.01
2 nd	826	888	< 0.01	239	0.26
3 rd	450	48	0.91	775	< 0.01
1 st - 3 rd	450	2,280	0.01	1,991	< 0.01

These data demonstrate there are programming or developmental events being affected in early life that have a lifetime impact on productivity. When we evaluated the 450 animals that had completed a third lactation, we found a lifetime milk effect of pre-weaning average daily gain of over 6,000 lb of milk depending on pre-weaning growth rates. Further, 22% of the variation in first lactation milk production could be explained by growth rate prior to weaning. This suggests that colostrum status and nutrient intake and or pre-weaning growth rate have a greater effect on lifetime milk yield and account for more variation and progress in milk yield associated with the management of the calf than genetic selection. Generally, milk yield will increase 150 to 300 lbs per lactation due to selection whereas the effect of management is three to five times that of genetic selection.

In the Cornell herd, the effect of diarrhea or antibiotic treatment on ADG was not significant and ADG differed by approximately 30 g/d for calves that had either event in their records ($P > 0.1$). However, for calves that had both events recorded, ADG was lower by approximately 50 g/d ($P < 0.01$). Over the eight year period, approximately 59% of all of the calves had at least one of the recorded events.

In the data from the Cornell herd, first lactation milk yield was not significantly affected by reported cases of diarrhea. Antibiotic treatment had a significant effect on TDM residual milk and calves that were treated with antibiotics produced 1,086 lb less milk in the first lactation ($P > 0.01$) than calves with no record of being treated. Regardless of antibiotic treatment, the effect of ADG on first lactation milk yield was significant in all calves ($P < 0.05$). Calves that were treated with antibiotics produced 1,373 lb more milk per kg of pre-weaning ADG while calves that did not receive antibiotics produced 3,101 lb more milk per kg of pre-weaning ADG. The effect of increased nutrient intake from milk replacer was still apparent in the calves that were treated, but the lactation milk response was most likely attenuated due to factors associated with sickness responses and nutrient partitioning away from growth functions (Johnson, 1998; Dantzer, 2006).

An analysis of all the lactation data and the pre-weaning growth rates, when controlled for study, suggests that to achieve these milk yield responses from early life nutrition, calves must double their birth weight or grow at a rate that would allow them to double their birth weight by weaning (56 days). This further suggests that milk or milk replacer intake must be greater than traditional programs for the first 3 to 4 weeks of life in order to achieve this response.

The papers and data described in Table 1 were analyzed in a meta-analysis to further investigate the impact of nutrient intake and growth rate prior to weaning (Soberon and Van Amburgh, 2012). The analysis excluded Foldager and Krohn, (1991) due to inadequate data and Davis-Rincker et al. (2011) because they did not measure full lactations. The Morrison et al. (2009) study was included in the analysis). The software used was Used Comprehensive Meta Analyses software (www.Meta-Analysis.com) (Borenstein et al. 2005) and the data included were study, treatment size (number of calves) mean milk yield, standard error or deviation, P value and effect direction. The data of Soberon et al. (2012) was initially excluded and then included to test for weighting effects since Soberon et al. contains many hundreds of animals. Inclusion of Soberon et al. did not change the outcome and the data were included in the analyses. The analysis indicated that feeding higher levels of nutrients from milk or milk replacer prior to weaning significantly increased milk yield by 959 ± 258 lb, $P < 0.001$, with a confidence range of 452 to 1,463 lb of milk. Further, if ADG was included as a continuous variable among the data set, the outcome was similar to that of Soberon et al. (2012) where for every pound of pre-weaning ADG, milk yield in the mature animal increased by 1540 lb ($P = 0.001$).

What changes in the animal are allowing for these differences? There is no one answer to that question but investigations are looking for several factors. Although mammary development as previously measured is probably not the appropriate factor (Meyer et al., 2006a, 2006b), it is intriguing to look at very specific cells within the mammary gland. There are a couple sets of data that demonstrate increased mammary cell growth based on early life nutrient intake. Brown et al.

(2005) observed a 32 to 47% increase in mammary DNA content of calves fed approximately 2 versus 1 pound of milk replacer powder per day through weaning. Just like the milk production increases discussed earlier, this mammary effect only occurred prior to weaning. In fact, this increase in mammary development was not observed once the calves were weaned, indicating the calf is more sensitive to level of nutrition prior to weaning and that the enhancement mammary development cannot be "recovered" once we wean the animal.

Meyer et al. (2006a) observed a similar effect in mammary cell proliferation in calves fed in a similar manner. The calves on their study demonstrated a 40% increase in mammary cell proliferation when allowed to consume at least twice as much milk replacer as the control group before weaning (Meyer et al., 2006a). Sejrsen et al (2000) observed no negative effect on mammary development in calves allowed to consume close to ad libitum intakes. A more specific attempt to look at stem cell proliferation did not find increased stem cells in calves fed higher levels of nutrient intake (Daniels et al., 2008) and it was hypothesized that the stem cell proliferation might lead to greater secretory cells once the animal becomes pregnant.

Economics

An in depth economic analyses of a program designed to double the birth weight and decrease age at first calving by almost 3 months was conducted by Dr. Mike Overton with input from Dr. Bob Corbett (Overton, 2010). In his analyses he utilized both research and herd data to characterize the costs and potential income associated with feeding and managing calves in a manner to promote a milk yield response. In his analysis, the first lactation profit was \$190 per heifer without accounting for the increase in inventory and what that means to changes in either voluntary culling or heifer sales. The change in profitability was due to the average 1,700 lb milk response observed from the studies described in Table 1 and was adjusted for net present value of the investment today relative to the income two years from now.

We conducted our own analysis of the response using calf and heifer performance data from a herd used in a heifer cost benchmarking study from New York (Table 3). There are many terms for the difference in management of the calves – in this analyses we will call it intensified but it really represents more biologically normal growth. Actual health data, feed costs and total costs of rearing were included in the estimation. Age at first calving was a function of getting heifers pregnant at 55% of the mature body weight and then calving at a minimum of 82% in both systems. In our analyses, AFC was reduced by 2.3 months, but the costs associated with achieving the same body weight post calving were nearly identical due to the higher costs of feeds and the amount of feed consumed to achieve the earlier AFC.

While the cost per heifer completing the system did not change, there are several other areas where there is economic value associated with the decreased calving age and the decrease in non-performance expense. If at the start the same number of heifer calves each month, there will be on average 2 more animals completing the system each year. There is also a decrease in the total number of animals in the replacement program, dropping 8%. This could allow the dairy to grow larger with the same replacement system, or allow the dairy to investment in a replacement program that was 8% smaller than before. The third area to impact profitability is the increased performance of the heifer in the dairy herd.

Using a model that treats the replacement program as a separate enterprise within the dairy, we looked at the combined changes for this herd, decreasing the calving age to 22.2 months, decreasing the non-performance rate to 7.5%, and fully transferring the increased value of production in the lactating herd. The non-completion rate was reduced due to a reduction in death loss with greater nutrient intake prior to weaning with no changes post-weaning, indicating there will be more heifers available to enter lactation. The base replacement enterprise was generating a

return of 0.87% on assets invested in the replacement program. With all the changes, the return increased to 7.2% (Table 4).

Table 3. Cost assessment of conventional versus intensified calf and heifer programs.

	Conventional	Intensified
Pre-weaning cost per pound gain, \$	2.73	2.91
Total pre-weaning gain, lb	64	102
Age at pregnancy, mo.	15.4	12.2
Age at first calving, mo	24.5	22.2
Overall average daily gain from birth, lb	1.70	1.89
Body weight at calving, lb	1,350	1,350
Percent non-completion rate, % entering replacement program	10.2	7.5
Total cost per heifer, \$	1,738	1,740
Total investment per heifer, \$	1,887	1,890

Table 4. Replacement enterprise impact for selected management changes for a 250 cow herd. These values represent the differences in expenses associated with the heifer rearing enterprise associated with the calf raising program.

	Base	Lower Calving Age	Lower Non-Completion Rate	Combined Changes
Heifers to cows ratio, %	76	68	74	69
Total rearing costs, \$	1,736	1,739	1,701	1,724
Income per animal, \$ Completing system	1,900	1,900	1,900	2,104
Total investment, \$	223,142	202,348	217,508	211,692
% Return on Capital	0.87%	0.53%	1.75%	7.27%

The profitability increase is due to the potential decrease in inventory due to calving approximately 3 months earlier and the milk yield increase due to improved nutrition and management from birth. The management decisions associated with the inventory change due to AFC are difficult to generalize among all herds and it is really a one-time adjustment to the cost of production. However, given the potential change in milk yield over the life-time of the animal, the change in calf management in a program that maintains the targets throughout the growing phase is worth approximately \$211, assuming a discount of 7% per year over the three year period, a \$15 milk price, an income over feed costs of \$10.50. This value is similar to the profit calculation of Overton (2010) and an outcome of the average milk response we are using to make the estimation along with the individual assumptions about costs of management.

Summary

Early life events have long-term effects on the performance of the calf. Our management approaches and systems need to recognize these effects and capitalize on them. We have much to learn about the consistency of the response and the mechanisms that are being affected. Given the amount of variation accounted for in first and subsequent lactation milk yield, there are opportunities to enhance the response once we know and understand those factors. The bottom line is there is a positive economic outcome to improving the management of our calf and heifer programs starting at birth.

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