TRANSFER OF INSULIN-LIKE GROWTH FACTOR-I FROM COLOSTRUM TO SYSTEMIC BLOOD OF HOLSTEIN NEONATES

By

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Some people come into our lives and quickly go.

Some stay for a while and leave footprints on our hearts.

And we are never, ever the same.

Author unknown

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CHAPTER I

INTRODUCTION

Cattle lack placental transfer of immunoglobulins, and for this reason ingestion of colostrum immediately following birth is crucial for the survival of a calf. Colostrum, the first milk a cow produces following calving, contains many components including immunoglobulins, growth factors and proteins. Because calves are able to absorb immunoglobulins across the small intestine, it has been speculated that other molecules may also be absorbed.

When calves are born their digestive system functions very similar to a nonruminant, as the calf ages the rumen begins developing. When a calf's rumen is developed then the calf can be weaned off of milk. This time period from birth to weaning is very labor intensive and costly for dairy farmers. Advancing the development of the gut of the neonatal calf would be very advantageous allowing calves to be weaned earlier. Insulin-like growth factor-I (IGF-I) is present in colostrum and several studies have shown that IGF-I stimulates the small intestine of neonates. However, there have been conflicting findings as to if IGF-I is truly absorbed by the neonate. Thus the purpose of this study was to determine if there was an increase in IGF-I in the systemic circulation of neonatal calves corresponding to the concentration of IGF-I administered in the colostrum.

CHAPTER II

REVIEW OF LITERATURE

COLOSTRUM

To a dairy producer, raising heifer calves to replace cows in the milking herd is an economical necessity. Because newborn calves have a high mortality rate during the first week of life, especially during the first 36 h of life, raising replacement heifers is a challenge (McCoy et al., 1970). Mortality rates have been reported to be 3.2 % in studies of more than 3000 calves (Tyler et al., 1999) and as high as 21 % in some herds (Nocek et al., 1984).

High mortality rates have been attributed to the lack of adequate colostral management early in the calf's life. Due to the lack of placental transfer of immunoglobulins calves are born with less than 10% of the immune resistance needed to protect them from disease (Nocek et al., 1984; Quigley and Drewry, 1998). Consequently, the calf is born without adequate humoral immunity and is almost entirely dependent on the passive transfer of maternal immunoglobulins from colostrum after birth. This acquisition of passive immunity is critical to calf survival; therefore, calves must be fed colostrum to receive needed antibodies.

Contents of Colostrum

Colostrum is the first milk a cow produces after parturition. Colostrum is lower in lactose but has more fat, protein, peptides, fat-soluble vitamins, minerals, hormones, growth factors, nucleotides, polyamines, and cytokines than mature milk (Rauprich et al., 2000). These substances are important for cellular growth and differentiation and influence gastrointestinal tract functions, metabolism, immune reactions, and endocrine systems in newborn animals (Koldovsky, 1989; Quigley and Drewry, 1998). Calves that have not been fed colostrum early in life are more susceptible to bacterial invasion as well as more vulnerable to diseases such as septicemia (Corley et al., 1977).

An immunoglobulin (Ig) refers to a family of high molecular weight proteins which share common physio-chemical characteristics and antigenic determinants (Butler, 1969). Molecules with antibody activity are included in this group as well as other chemically related normal or pathological proteins (Butler, 1969). These proteins are not classified by the antibody specificity, but rather by the phyiso-chemical and antigenic characteristics (Butler, 1969). Colostrum includes IgG, IgM, and IgA as the different immunoglobulins. The most studied and abundant immunoglobulin in the dairy cow belongs to the class IgG. At least 85 to 90% of the serum and whey immunoglobulins are of this class (Klaus et al., 1969). Various Igs augment the recognition and phagocytosis of bacteria by leukocytes, prevent the adhesion of microbes to surfaces, inhibit bacterial metabolism, hinder bacteria, and neutralize toxins and viruses (Korhonen et al., 2000). IgM is a macroglobulin comprising of less than 10% of the serum and colostral immunoglobulins (Klaus et al., 1969). IgM have much of the same functions as IgG. Although IgM is present in much smaller amounts than IgG, it is much more efficient in

the fore mentioned activities (Korhonen et al., 2000). IgM contains 12.3 % carbohydrate, IgG contains 2-4% carbohydrate, whereas the third immunoglobulin, IgA, contains 8-9% (Klaus et al., 1969). IgA does not fix complement or oppose bacteria but terminates antigens, neutralizes viruses and bacterial toxins, prevents the adhesion of enteropathogenic bacteria to mucosal epithelial cells, and is resistant to the activities of proteolytic enzymes (Korhonen et al., 2000).

Colostrum varies from milk in the contents of total solids/dry matter (DM), and ash (Oyeniyi and Hunter, 1978). The percentage of total solids found in colostrum is about 25% compared with 13% in normal milk (Oyeniyi and Hunter, 1978). Oyeniyi and Hunter, (1978) speculated that the DM in colostrum would have an effect on the movement of water in the digestive tract. They used osmotic pressure differences as an explanation. If the Igs are absorbed intact from the colostrum then the water in the intestinal cells could be replacing the absorbed protein (Oyeniyi and Hunter, 1978). The total lactose concentration in the colostrum is lower than that of normal milk (Parrish et al., 1950). This is probably important since lactose can make a calf scour (diarrhea) which can result in death or unthriftiness (Bywater and Penhale, 1969). The ash of milk primarily includes K, Ca, Na, Mg, and Fe as cations and P, Cl, and S as anions (Oyeniyi and Hunter, 1978). Several essential minerals are increased in milk at parturition including calcium, which is needed for bones and teeth, and phosphorus, also needed for bone and teeth development in addition to energetic metabolism and metabolic functions. In addition, Garrett and Overman (1940) found Mg, Na, and Cl in milk also high at parturition with potassium being low at parturition and gradually increasing. Parrish et al. (1950) found that the protein secreted in colostrum decreased to 84% of the amount

found at parturition by 12 h and by 24 h it had decreased to 64% of the proteins found in colostrum at the time of calving.

Colostrum also has high concentrations (i.e., 201 to 385 ng/ml) of insulin-like growth factor-I (IGF-I) (Hammon et al., 2000; Rauprich et al., 2000), indicating that newborn calves may receive large quantities of IGF-I (Baumrucker and Blum, 1994). This hormone increases GI tract development and function in neonatal calves and pigs (see later section "Functions of IGF-I within the GI tract"). Concentrations of IGF-I increase in mammary secretions while the concentration of IGF-I in the plasma decreases during the last 4 weeks of pregnancy (Baumrucker and Blum, 1994) and may account for higher levels of IGF-I found in colostrum versus normal milk. Whether IGF-I or other proteins are absorbed by the neonatal gut is discussed in a later section (see "Absorption of Gut Peptides"). In the following section factors affecting absorption of Igs will be discussed with the intent to understand the timing of closure of the gut to large proteins.

Factors Affecting Absorption of Igs

The bulk of colostral Igs found in the neonatal calf come from active transport of plasma across the alveolar epithelium (Butler, 1969). Stott et al. (1979a) looked at the different absorption rates of Igs. All three of the Igs had the same mean closure time of the absorption period. However, the time of the first feeding had an effect on the closure time of the various Igs. Stott and Fellah (1983) found a quadratic response in the absorption of IgM and the volumes fed. The higher the concentration of IgM fed the lower the efficiency of absorption. IgM has been shown to have a slower transfer rate,

likely because of the greater molecular size of IgM (1,000,000) when compared to IgG and IgA (150,000 and 170,000, respectively) (Stott et al. 1979b).

When first feeding is delayed, gut closure is also delayed (Selman et al., 1971; Stott et al., 1979a). While this and other factors may increase the amount of time absorption occurs they do not replace the amount that could have been absorbed if a calf had been fed at 0 h. According to Stott et al. (1979a), 50% of the calves whose colostrum intake was delayed to 24 h after birth did not absorb Igs, suggesting that the critical period of absorption had passed before calves were exposed to colostrum. However, delaying feeding of calves up to 8 h was found to have no effect on the ability of calves to absorb Ig (Todd and Whyte, 1995). Michaneck et al. (1989) concluded acceptable passive immunity can be achieved in calves which do not receive their first colostrum immediately after birth if you feed a quantity of Ig that will allow the calf the opportunity to utilize fully its transmission capacity for the first feeding.

Stott et al. (1979a) reported a positive correlation between the absorption of IgG and IgM, but the absorption of IgA was not correlated to either IgG or IgM. In addition, there was a significant positive linear response between the amount of IgA in the colostrum and the amount absorbed. A negative correlation was found with the amount of IgM in colostrum and the efficiency of absorbency as well as the amount of IgG in the colostrum and the efficiency of absorption (Besser et al., 1985). Efficiency of absorption was determined by [(Peak serum Ig concentration) (0.07 BW^3)(100 %)] / [(Colostrum Ig concentration) (L of colostrum fed)] (Besser et al., 1985). Besser et al. (1985) indicated the similar negative correlation in IgG and IgM efficiency of absorption and amount of Ig in colostrum suggest that IgG and IgM share a mechanism of absorption and that these

mechanisms could include a shared macromolecular transport system across the calf intestinal epithelium or a regulation of the Ig concentrations in calf serum. Further work is needed to verify if there is a shared macromolecular transport system between IgG and IgM in cattle. Also, the idea that the concentration of Ig in serum reaches a maximum and absorption ceases has been demonstrated in humans and mice, but not cattle (Boyd, 1972), and thus requires further investigation.

The mechanism for macromolecular absorption in pigs has been identified by the ingestion of colostrum stimulating intense pinocytotic activity in the intestinal epithelial cells (Broughton and Lecce, 1970). The closure, or the halt of cellular uptake of macromolecules, occurs when the plasmalemma of the intestinal epithelial cells make contact with the ingested nutrient and the digestive fluid (Lecce, 1973). Stott et al. (1979b) speculated this contact would stimulate the cells to cease their pinocytotic activity and the uptake of the macromolecules would cease. However, the continued increase of Ig levels can be attributed to the fact that systemic circulation continues until the cellular contents are exhausted (Stott et al., 1979b). The idea that ingested colostrum stimulates pinocytotic activity in intestinal epithelial cells further explains the importance of having sufficient colostrum intake at the first feeding to excite and satiate all potential absorptive cells lining the walls of the small intestine (Stott et al., 1979b). A greater volume of colostrum would be needed to activate all of the possible pinocytotic epithelial cells so all cells could absorb Ig. In contrast, Stott and Fellah (1983) found that when calves were fed one liter at 100 mg/ml and two liters at 50 mg/ml Ig, both having the same mass, the calves fed one liter showed greater absorption. Hopkins and Quigley (1997) reported no difference in IgG absorption when calves were fed 3 L in one feeding

or split between 2 feedings 12 h apart. Furthermore, if the Ig concentration is low, then inadequate absorption of Ig will occur regardless of volume (Stott and Fellah, 1983).

Several factors in addition to timing and amount of colostrum intake can have an influence on the absorption of the constituents of colostrum. Among these is the effect of the method of colostrum intake. Adams et al. (1985) looked at the effects of feeding by an esophageal tube or a nipple bottle. There was no effect on the rate of absorption of IgG during the first 12 h based on the method of feeding. Adams et al. (1985) found that feeding calves via an esophageal tube was an effective method of administering colostrum to calves that were reluctant to nurse or too weak to nurse after birth. Besser et al. (1991) looked at the effects of an esophageal tube, a nipple bottle, and suckling. The failure of passive immunity transfer for the 3 methods were 10.8% for the esophageal tube, 19.3% for the nipple bottle, and 61.4% for the calves who suckled. Several other studies have shown calves that suckle to have a higher risk of failure of passive transfer (Brignole and Stott, 1980; Besser et al., 1985). Besser et al., (1985) suggested this lack of passive transfer could be due to the calf not ingesting enough colostrum. Similarly, the nipple bottle and esophageal tube fed calves that showed low immunity absorption was attributed to the calves not getting enough colostrum in the first feeding. In a study by Bringnole and Stott (1980) on 983 dairy calves, only 57.8% of calves left with their dams 12 to 26 h postpartum had detectable IgG and IgM concentrations indicating they had suckled. When the calves were separated from their dams and bottle fed colostrum, the serum Ig concentrations increased, with the proportion of nonabsorbent calves increasing linearly with the higher level of Ig concentration before bottle feeding (Bringole and Stott, 1980). Conversely, Stott et al. (1979c) reported that the suckled

calves in their study had nearly double the mean absorption rate as those fed by bottle, and this increase in absorption rate continued through the second and third feedings. The major factor for the differences in absorption of Ig in suckling calves can be attributed to the age at initial feeding and the amount of colostrum fed.

Stott et al. (1979c) theorized it was possible that milk from the teat cistern and the gland cistern, the first milk a calf would ingest when suckling, may have a higher concentration of Ig than colostrum produced at the initiation of milk letdown by the alveolar tissue. Subsequently, Stott et al. (1981) evaluated the location of milk, teat cistern and gland cistern vs. alveolar tissue on the concentration of Ig. A partial milking which included 100 ml stripped from each quarter to measure the Ig levels in the teat cistern and gland cistern was taken and then a complete milking, following the stripping, which collected the remainder of the milk produced after milk letdown was performed. The concentrations of Ig between these two milkings did not differ significantly (Stott et al., 1981). Further analysis showed a 50% decrease in the concentrations of each of the three Ig levels with subsequent milkings (Stott et al., 1981). Due to these findings further investigation as to the possible causes of differing Ig levels in suckling calves is needed.

Another possible cause of differing Ig levels in colostrum is the age or parity of the cow. Oyeniyi and Hunter (1978) found that the levels of IgG present in Holstein colostrum did not differ from cows in their first, second, or third lactation, however, cows beginning the fourth through seventh lactation had more IgG in their colostrum. In addition, the younger animals also had a faster rate of IgG disappearance from the first three milkings of colostrum. The average total Ig in colostrum during the first 4 d have been found to differ by as much as 255 g in first lactation cows and 2029 g of Igs in

second lactation cows (Devery-Pocius and Larson, 1983). Younger animals have less mammary gland development and a lower amount of Ig in the colostrum. This could be due to lower serum Ig concentrations and less capacity for transport in heifers versus mature cows suggesting that the Ig transport system may mature as the mammary glands mature (Devery-Pocius and Larson, 1983). Pritchett et al. (1991) found a positive correlation in the weight of the first milking and the total amount of IgG found in colostrum. From these studies it can be concluded that greater concentrations of Ig can be found in colostrum of multiparous versus primiparous cows.

Other lactational factors such as length of the dry period, and time between calving and first milking have also been studied. The length of the dry period for second lactation and mature cows was found to be significantly correlated to the weight of the colostrum from the first milking (Pritchett et al., 1991). Besser and Gay (1991) showed similar results with calves fed colostrum from cows with long dry periods having a lower risk of developing passive immunity.

Environmental or seasonal factors may impact the quality of colostrum. Shearer et al. (1985) found mean colostrum scores tended to be higher in August, September, January, and February when studied over a whole year in Florida. Similarly, a study by Gay et al. (1983) at Washington State University found the highest serum Ig values in July, August, and September, and the lowest in January and February. At the University of Guelph-Elora Dairy Research Center (Burton et al., 1989), significantly higher concentrations of IgG in colostrum were obtained from cows in the spring and fall than in the winter. Seasonal changes in colostral Ig concentration have also been studied by exposing pregnant heifers to high air temperatures (Nardone et al., 1997). While the

colostrum yield in these heifers did not differ, the colostrum composition was affected by high air temperatures (Nardone et al., 1997), suggesting that stress impaired the transfer of Ig from the blood stream to the udder. While the study by Nardone et al. (1997) states colostral Ig levels in the heifers exposed to high air temperature were not below what they considered the required minimum for Ig concentration, environment did have an effect. Olson et al. (1981) showed an increase in IgM levels in the serum of calves exposed to cold compared to those kept in a 21°C environment. Olson et al. (1981) stated that moderate cold stress with no change in core body temperature has minimal effects on intestinal absorption. Collectively, these studies indicate the quality of colostrum is best during late summer (August, September) and late winter (January, February).

The breed of cattle can have an effect on overall milk production, and milk fat and milk protein content; similarly breed may have an effect on the Ig concentration in colostrum. Muller and Ellinger (1981) compared Ayrshire, Brown Swiss, Guernsey, Holstein, and Jersey colostrum to see the differences in Ig content. The average total Ig content in colostrums was 8.1% for Ayrshire, 6.6% for Brown Swiss, 6.3% for Guernsey, 5.6% for Holstein, and 9% for Jersey cows the latter of which had the highest individual concentrations of IgG, IgM, and IgA. Similarly, Tyler et al. (1999) found Guernsey colostrum to have greater IgG concentration than Holstein colostrum. Guernsey colostrum had the lowest concentrations of IgM and IgA. Health problems and high mortality rates have been reported with Guernsey calves and may be related to the low IgA and IgM values (Muller and Ellinger, 1981). In contrast, Newstead (1976) found Holstein colostrum has an average Ig concentration 1.5 times that of Jersey colostrum.

These differences can partially be attributed to differences in management. For example, the cattle of Newstead (1976) were allowed to be suckled before samples were taken. Further research is needed in the area of breed differences in Ig concentrations. However, it is difficult to find large enough herds of different breeds with similar management practices to examine the possible effects.

A means of identifying a calf that has consumed adequate Ig on the farm is difficult aside from waiting on a calf to become ill. Parish et al. (1997) studied if the serum gamma glutamyltransferase (GGT) levels could be used to predict the serum IgG concentration. GGT is an enzyme produced by the mammary ductile cells which aids in amino acid transport (Baumrucker, 1979). Calves are born with negligible GGT activity; the bulk of calf serum GGT is colostral derived (Parish et al., 1997). Hammon and Blum (1997) found GGT activity significantly increased after colostrum intake and GGT values remained unchanged when calves were fed milk replacer instead of colostrum. An increase in serum GGT due to dehydration would parallel the degree of hemoconcentration (Parish et al., 1997). Total serum protein concentrations can be affected by dehydration since other plasma analytes such as glucose, urea, and creatinine can contribute to the refractive index (Perino et al., 1993). Total serum protein includes both the immunoglobulin as well as the nonimmunoglobulin serum proteins (Parish et al., 1997). Perino et al. (1993) and Parish et al. (1997) both determined that the serum GGT level is a useful test for passive transfer of colostral immunoglobulins in neonatal calves.

Insulin-Like Growth Factor (IGF)-I

Chemical composition

Insulin-like growth factor-I (IGF-I) is a polypeptide chain 70 amino acids long and containing three intrachain disulfide bonds (Griffin and Ojeda, 1992). The basic structure of the IGF-I gene is fairly simple, however every species has some degree of additional complexity with the mammals perhaps being the most complex (LeRoith and Raizada, 1993). The structure of IGF-I is highly homologous (i.e., > 99 %) among farm animals (Spicer and Echternkamp, 1995) and resembles proinsulin from which insulin is derived (Griffin and Ojeda, 1992). The C peptide region is cleaved from proinsulin during the formation of insulin but not during the formation of IGF-I (Griffin and Ojeda, 1992). Twenty-five out of the 51 amino acids found in the A and B chains as well as the disulfide bonds of insulin are identical to the amino acids found in IGF-I (Griffin and Ojeda, 1992). In addition, a region called the D domain adjoins to the A chain (Ganog, 1995). Differences in these two molecules include differences in the C peptide region where insulin contains more amino acids, and at the carboxy-terminus end where IGF-I has an additional 8 amino acids (Griffin and Ojeda, 1992).

Factors Affecting the Production and Release of IGF-I

IGF-I is a key regulator in growth (Davis, 1988; Noguchi, 2000) and reproduction (Spicer and Echternkamp, 1995; Yoshimura, 2000). IGFs are synthesized by most cell types and organs of the body including liver, cartilage, muscle, mammary, and adipose tissue with the liver being the main source of circulating IGF-I (Griffin and Ojeda, 1992; LeRoith and Raizada, 1993; Ganong, 1995). The level of IGF-I found in an animal is

mainly regulated by growth hormone (GH) and dietary intake, but can be influenced by other hormones such as estradiol and glucocorticoids (Adamo et al., 1994). Increases in GH causes decreases in IGF-I and contrariwise. However, nutritional deprivation causes dramatic decreases in IGF-I along with increases in GH (Breier et al., 1986). Several different types of cells both secrete IGF-I and contain receptors for IGF-I indicating this hormone operates locally (Griffin and Ojeda, 1992). An autocrine mechanism is when a cell can both secrete a hormone and react to the same hormone through receptors found in the cell, and in this way is able to amplify the hormone's signal to the cell (Griffin and Ojeda, 1992).

As mentioned, nutritional status of an animal has a large impact on the amount of circulating IGF-I. IGF-I has been shown to be an indicator for undernutrition in cattle (Richards et al., 1995), calorie or protein restriction can inhibit IGF-I (Davis, 1988). An increase in circulating IGF-I and decrease in GH are associated with improved nutritional status (Bossis et al., 2000; Lalman et al., 2000). When protein is in excess, decreasing dietary energy may not decrease plasma IGF-I significantly (Enright et al., 1994) since IGF-I has been shown to regulate body protein metabolism (Noguchi, 2000). In neonatal calves, the amount of colostrum fed as well as other nutritional factors affect IGF-I levels in blood (Hammon et al., 2000). Thus, the concentration of systemic IGF-I may be used to determine if cattle, regardless of age, are nutritionally deprived.

In cattle, IGF-I is found bound to specific IGF binding proteins (IGFBP) in blood and follicular fluid (Spicer and Echternkamp, 1995) and colostrum (Campbell et al., 1991). Like IGFs, the IGFBPs are influenced by the nutrition, specifically the energy and protein levels as well as endocrine factors such as GH, glucocortocoids, and insulin

(Noguchi, 2000). These IGFBPs are thought to both inhibit and stimulate the action of IGF depending on cell type (Spicer and Echternkamp, 1995; Collett-Solber and Cohen, 2000; Yoshimura, 2000).

Functions of IGF-I within the GI tract

The development of the small intestine of a calf is largely dependent on protein and energy intake (Buhler et al., 1998). IGF-I has been proposed to have a stimulating effect on the small intestine of neonates. With the high mortality rate in calves, advancing the development of the small intestine could be extremely beneficial to the development of the calf. For these reasons, this section of review will examine the possibility of IGF-I absorption in neonates.

When IGF-I was added to milk replacer and fed to suckling calves, gastrointestinal mucosal growth and brush-border enzymes were stimulated (Baumrucker et al., 1994). Similarly, enzymes in the jejunum increase significantly in 14-d old rats given IGF-I orally while brush border enzyme activity in the duodenum and ileum were not significantly altered (Young et al., 1990). Buhler et al. (1998) summarized that colostrum feeding in calves stimulates changes in small intestinal villus size in calves, and that in calves fed colostrum for 6 d, more cells were leaving the crypts and moving toward the tips of the villi. Calves fed colostrum for 6 d had increased villus height versus those fed colostrum for one day or those fed only milk replacer (Buhler et al., 1998). Calves fed colostrum for one day also had slightly higher villus heights than those fed milk replacer (Buhler et al., 1998). In 13-d old rat pups, wet tissue weights of all gastrointestinal components increased after IGF-I administration via osmotic pumps

beginning on d 6 (Steeb et al., 1997). Specifically, IGF-I increased the mucosal thickness with increases in villus height of 22% and crypt depth up to 28% in rat pups (Steeb et al., 1997). Buhler et al. (1998) reported that colostrum feeding of 8-d old calves influenced the duodenum more than the distal parts of the gut. Steeb et al. (1997) also found the proximal intestine was more responsive to IGF-I treatment in 6 -to 19-d old rat pups. Interestingly, IGF receptors in developing rat intestines are more predominant in the jejunum and bind 2.5 to 5 times greater than in adult rat tissue (Young et al., 1990). Baumrucker et al. (1994) found that the number of IGF receptors in the intestinal mucosa of calves increased after feeding IGF-I. Thus, studies in both cattle and rats indicate that intestinal mucosa have receptors for IGF-I and respond to systemic and oral increases in IGF-I levels.

Conversely, Alexander and Carey (1999) found the oral administration of IGF-I to 4-d old piglets had no significant effect on mucosal weight, villus height, or crypt depth in the jejunum and ileum. Alexander and Carey (1999) attributed the lack influence of IGF-I on intestinal growth to the fact that the neonatal pigs used in their experiment were healthy with adequate nutrition allowing for maximal intestinal growth rates. Although the IGF-I did not alter intestinal growth in the piglets it did appear to increase the active ion transport across the epithelium in the basal state (Alexander and Carey, 1999). Burrin et al. (1996) suggested that gastrointestinal protein synthesis in piglets is stimulated by nutrition with only a small part of this being due to non-nutritive components, including IGF-I. However, when piglets were fed sevenfold greater IGF-I than typically ingested from colostrum there was increased mucosal thickness and a lengthening of villus, but no increase in crypt depth (Burrin et al., 1996). The duration of IGF-I treatment may

influence the specific intestinal response observed. Several studies in other species (e.g., cattle) in which IGF-I effects on gut function have been observed were conducted over a shorter period of time (Baumrucker et al., 1994). In addition, other components of colostrum such as growth factors and binding proteins may affect the absorption or stimulating abilities of colostral IGF-I (Baumrucker et al., 1994).

Methods used to Detect IGF-I

The isolation of IGFs for lab analysis becomes difficult due to their binding affinity to the IGFBPs. These IGFBPs must be removed before IGF concentration can be measured. IGFBP-3, the largest molecular weight IGFBP, must be effectively removed to allow the IGF-I antibody to become the preferred binding partner of IGF-I. The lower molecular weight IGFBPs do not compromise the validity of IGF-I values measured (Crawford et al., 1992). These binding proteins have a higher affinity for IGF-II as opposed to IGF-I as was shown by the parallel lines of samples to standard curves in studies which have shown the lower binding proteins remaining after extraction (Crawford et al., 1992). Many methods have been examined to eliminate the IGFBPs from biological samples to allow for the measurement of IGF-I. When comparing the methods of treatments, acid-ethanol extraction has been one of the most common methods studied. Acid ethanol extraction has been validated for the recovery of IGF-I from the blood plasma of several species including fetal and adult sheep, rat, mouse, and man (Breier et al., 1991). Serum samples iodinated with 0.5 mCi $Na^{125}I$ and 2.5 μg chloramine T resulted in displaced curves parallel to the IGF-I standard for both acid-incubated serum and acid-ethanol extraction (kept at 25°C for 30 min) (Lee and Henricks,

1990). Concentrations of IGF-I in serum samples were 30% less using the acid ethanol extraction as compared to acid gel filtration (Lee and Henricks, 1990). High-performance liquid chromatography (HPLC) was used as a standard by Crawford et al. (1992), acid-ethanol extraction (at 4°C for 2 h) gave results comparable to HPLC. However, Gutierrez et al. (1997) found IGF-I to be present in excess to IGFBP, resulting in false positive estimates of IGF-I after acid-ethanol extraction (incubated for 30 min at 25°C). In attempts to increase the amount of IGF-I recovered samples can be incubated for 1 h at –20°C to form a second protein pellet. This method is called cryo-precipitation and increased recovery of ^{125}I-labeled rhIGF-I (recombinant IGF-I produced by yeast fermentation), when samples were incubated for 30 min at 25°C (Breier et al., 1991). Cryo-precipitation created a completely parallel line when compared to rhIGF-I and IGF-I (Breier et al., 1991). However, Gutierrez et al. (1997) also examined the cryo-precipitation performing the incubation at –20°C for 2 h, and found the recovery efficiencies for acid ethanol extraction (30 min at 25°C) and cryo-precipitaion did not significantly differ. Similarly, Crawford et al. (1992) found cryo-precipitation to be as effective as acid ethanol extraction at 4°C for 2 h. Acid ethanol extraction can be successfully used to separate the IGFPBs if conducted under certain conditions. Further investigation into the methods used to measure IGF-I show that with an incubation period of > 16 h at 4°C or > 4 h at 25°C caused a significant loss of IGF-I (Echternkamp et al., 1990). If serum samples were incubated for 16 h at 4°C values were 22% lower than with gel filtration but displacement curves were parallel to the standard curve (Echternkamp et al., 1990). If extraction is for 24 h at 25°C only 54% of added IGF-I was recovered, and this would cause an underestimation of actual IGF-I concentrations

(Echternkamp et al., 1990). Acid ethanol extraction is an acceptable method of isolation and quantification of IGF-I in bovine plasma and serum samples if the appropriate time and temperature for incubation are followed.

Absorption of Gut Peptides

The ability of the intestine to transport molecules across its border has been know since the absorption of Igs from colostrum was discovered. Before weaning, a neonate's intestine appears to be selectively hyperpermeable to large molecules (Gardner, 1984). However, in older animals the intestine acts more as a barrier preventing molecules from moving into systemic circulation (Gardner, 1984). Gut absorption of polypeptides has been demonstrated in neonatal rats (Thornburg et al., 1987). It has now been generally accepted that there is an uptake of particles across the border in animal models (Fasano, 1998). Also, peptides of two or three amino acid in length can be taken up via active transport through the brush border membrane (Fricker and Drewe, 1996). Otherwise, peptides attempting to enter the cell surface must cross the intestinal mucosal layer, which is 100 – 150 μm thick and excludes molecules above 600 – 800 Da (Fricker and Drewe, 1996). As mentioned earlier, IGF-I is 70 amino acids in length and 7,500 Da. When IGF-I is bound to IGFBP-3, as 75% of the IGF-I found in plasma is, it is approximately 150,000 Da (Jones and Clemmons, 1995). Therefore it is unlikely that IGF-I, free or bound to IGFBPs, are normally absorbed by the adult gut. Whether IGF-I (free or bound) can be absorbed by the neonatal gut when absorption of large proteins are possible (see previous discussion) is unclear. This section of review will summarize evidence for gut absorption of IGF-I

The question posed is: due to the intestinal permeability to macromolecules during the early neonatal period, can milk-borne growth factors be absorbed into the blood and affect the growth and metabolism of peripheral organs (Burrin, 1997). Vacher et al. (1995) catheterized the jejunum and mesenteric vein draining the jejunum in newborn calves and detected [^{125}I]IGF-I in the mesenteric vein of these calves after its administration, however, the absorption time of [^{125}I]IGF-I lasted only an hour. It has been shown that the feeding of colostrum results in a higher level of circulating IGF-I than in calves fed mature cow milk (Grutter and Blum, 1991), but whether this increase in IGF-I is due to IGF-I absorbed through the gut or due to some other factor is unclear. Plasma IGF-I levels decreased slowly after birth in calves fed colostrum with no supplemental IGF-I (Hammon and Blum, 1997). Baumrucker and Blum (1994) measured concentrations of IGF-I in newborn calves fed for 4 d: 1) milk replacer and colostrum derived globulin, 2) milk replacer and colostrum derived globulin and a recombinant human IGF-I, and 3) pooled colostrum. There was no difference in circulating IGF-I levels at 4 d in the calves fed the milk replacer and the globulin without IGF-I and the calves fed pooled colostrum. However, there was an increase in circulating IGF-I from the calves fed the recombinant human IGF-I seen at 4 d. This increase was suggested to be caused by the lack of IGFBPs in the milk replacer as opposed to the colostrum (Baumrucker and Blum, 1994). Vacher et al. (1995) lowered the pH of colostrum to below 5 to allow the release of IGF-I from its binding proteins. No increase in IGF-I absorption was seen suggesting other factors in colostrum may influence the absorption of IGF-I (Vacher et al., 1995). Hammon et al. (2000) stated that neonatal plasma concentrations of IGF-I are mainly influenced by the intake of colostrum (via

nutritional effect), because when first colostrum feeding was delayed calves showed decreased plasma IGF-I concentration. However, Lents et al. (1998) found that beef calves that had nursed exhibited decreased plasma IGF-I concentrations when compared to those which had not nursed. Plasma IGF-I concentrations in these beef calves remained constant between d 1 and 4 post-calving (Lents et al., 1998). Thus, the meager evidence in bovine neonates indicates that the gut may absorb dietary IGF-I. However, whether the gut of the bovine neonate absorbs endogenous IGF-I present in colostrum is still unresolved.

Because it is uncertain whether absorption of IGF-I from the colostrums occurs in neonatal calves, the present study attempts to determine if there is a relationship in the amount of IGF-I a calf consumes and the amount of IGF-I found in the serum of the calf. Unlike previous studies which have administered supplemental rhIGF-I this study will use colostrum and the naturally occurring levels of IGF-I to look for a relationship between the colostrum and the calf's serum concentrations of IGF-I.

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CHAPTER III

SERUM INSULIN-LIKE GROWTH FACTOR-I (IGF-I) CONCENTRATIONS AT BIRTH AND AFTER COLOSTRUM FEEDING IN HOLSTEIN CALVES: RELATIONSHIP WITH COLOSTRAL IGF-I

Abstract

Colostral IGF-I may be beneficial in the development of the gastrointestinal tract of the bovine neonate. Thus, the purpose of our study was to examine the relationship among concentrations of IGF-I in colostrum at the initial two feedings and serum concentrations of IGF-I, total protein, gamma glutamyltransferase (GGT), and IgG at 0 and 48 h after birth in Holstein neonates. Calves (n = 22) were separated from dams immediately after birth, pre-suckle blood samples were taken, and a second blood sample was taken at 48 h after birth. Calves were fed colostrum for 2 feedings and milk replacer thereafter. Linear regression of serum IGF-I at 48 h and colostral IGF-I revealed a significant positive ($r = 0.452$) relationship ($P < 0.05$). However, linear regression of colostral IGF-I and the difference in 48 h and 0 h serum IGF-I did not show a relationship ($P > 0.25$). Calves were assigned to Group 1 (0 h serum IGF-I < 10 ng/ml) or Group 2 (0 h serum IGF-I ≥ 10 ng/ml) for further analysis. There was no difference ($P > 0.25$) in serum IGF-I concentrations at 48 h between Group 1 (n = 11) and Group 2 (n = 11). Simple Pearson correlation coefficients revealed a negative relationship among serum IGF-I at 0 h and the difference between the serum IGF-I at 48 h and 0 h ($r = -0.824$) as well as body weight of the calf at birth and the amount of GGT at 48 h ($r = -0.604$). Sex of calf had no effect ($P > 0.10$) on plasma variables, but affected birth weight ($P = 0.0063$) with females having a lower birth weight than males. Total serum protein and

serum GGT concentrations were also correlated at 0 h (r = 0.573). Our study provides indirect evidence for absorption of IGF-I from the colostrum into the systemic circulation.

(Key Words: IGF-I, neonatal calves, colostrum)

Abbreviation key: GGT = gamma glutamyltransferase, **IgG** = immunoglobulin G, **IGF-I** = insulin-like growth factor-I.

Introduction

To a dairy producer, raising heifer calves to replace cows in the milking herd is an economical necessity. Because, newborn calves have a high mortality rate during the first week of life, raising replacement heifers is a challenge (McCoy et al., 1970). A lack of placental transfer of immunoglobulins in cattle produces calves that are born with a very low resistance to disease (for review see Quigley and Drewry, 1998). Thus, the bovine neonate must be fed the colostrum from its mother to receive the needed antibodies. Serum gamma glutamyltransferase (GGT) concentration in calves is a reliable measure of passive transfer of colostral immunoglobulins (Perino et al., 1993; Parish et al., 1997). Recent studies suggest other components/factors of colostrum, in addition to immunoglobulins, may be important to neonatal calf health (for review see Quigley and Drewry, 1998). One of these components is likely IGF-I (Baumrucker et al., 1994a; Burrin, 1997).

IGF-I is a key regulator of growth (Davis, 1988; Noguchi, 2000) and reproduction (Spicer and Echternkamp, 1995; Spicer et al., 2000). Nutritional status of an animal has a large impact on the amount of circulating IGF-I. Specifically, concentrations of IGF-I in

blood are indicators of undernutrition in cattle (Richards et al., 1995; Bossis et al., 2000), and calorie or protein restriction can inhibit IGF-I secretion (Davis, 1988; McGuire et al., 1992). The development of the small intestine of a calf is largely dependent on protein and energy intake (Buhler et al., 1998). In addition, IGF-I has been proposed to have a stimulating effect on the small intestine of neonates (Baumrucker et al., 1994a; Burrin, 1997). When IGF-I is added to milk replacer and fed to neonatal calves, gastrointestinal mucosal growth, brush-border enzymes, and intestinal DNA synthesis are stimulated (Baumrucker et al., 1994a). Hammon et al. (2000) concluded that concentrations of IGF-I in bovine neonates mainly are influenced by the intake of colostrum via a nutritional effect. With the high mortality rate in calves, advancing the development of the small intestine could be extremely beneficial to development and survival of the calf. However, whether endogenous IGF-I present in colostrum is absorbed by the gut of the bovine neonate is still unresolved. The objective of the present study was to determine whether the concentrations of IGF-I in colostrum, fed at the initial two feedings, affect concentrations of IGF-I in the systemic circulation of neonatal calves.

Material and Methods

Twenty-two Holstein dairy calves born at the Oklahoma State University Dairy Cattle Research Center between September 7, 1998 and November 9, 1998 were used. Calves were removed from dams immediately after calving and a pre-colostral blood sample was taken (0 h) from the jugular vein. Blood samples were collected in 5 ml tubes and refrigerated for 24 h. Serum was harvested after centrifugation at 1400 x g for 5 min and then stored at -20°C until assayed. Each calf received 2 L of colostrum from a nipple

bottle within 6 h of birth and again approximately 12 h later. Following the initial two colostrum feedings, calves were fed 2 L of milk replacer twice daily at 0800 h and 1700 h. For the initial two feedings, colostrum from the dam was used if possible, but a frozen reserve of colostrum was used if colostrum from the dam was unavailable. A sample of colostrum was taken from each of the first two feedings that each calf received and stored at -20°C. A second blood sample was collected via jugular venipuncture at 48 h (± 6 h); serum was harvested as described earlier. Calves were housed in individual calf hutches following birth.

The serum samples from each calf as well as colostrum samples of the first and second colostrum feedings were evaluated for IGF-I concentration. Samples were analyzed by radioimmunoassay after acid-ethanol extraction (16 h at 4°C) as described previously by Echternkamp et al. (1990). The intraassay coefficient of variation was 9.19%.

Quantification of IgG in the 48-h sample was done by radial immunodiffusion using a commercial kit from Triple J Farms (Bellingham, WA) (Kirkpatrick et al., 2001). Total serum protein and serum GGT concentrations were measured using Vitros Chemistry Products colorimetic tests according the manufacture's protocol (Johnson & Johnson Clinical Diagnostics, Inc., Rochester, NY).

Statistical Analysis

To determine if concentrations of IGF-I in colostrum during the first two feedings influenced serum IGF-I levels at 48 h or the change in serum IGF-I between birth and 48 h, linear regressions were performed. Mean colostral IGF-I concentrations were

calculated by averaging the IGF-I concnetraitions in the first two colostrum samples fed to each calf. Serum IGF-I at 48 h and the difference of serum IGF-I at 48 h and 0 h were used as dependent variables and colostral IGF-I concentration was the independent variable.

To determine if initial serum IGF-I levels affect the change in serum IGF-I levels between 0 and 48 h post-calving, data were arranged into two groups based on their pre-colostral serum IGF-I values. Calves with initial serum containing less than 10 ng/ml were assigned to Group 1 and those with concentrations greater than or equal to 10 ng/ml assigned to Group 2. These group values were based on the findings of Bossis et al. (2000) that indicated plasma IGF-I concentrations below 10 ng/ml exist in cattle under severe nutritional restriction. Main effect of Group and the interaction between time and Group were assessed by analysis of variance using PROC MIXED of SAS (1999). In addition, the effect of sex of calf on the serum IGF-I difference, serum variables at 0 h, and 48 h, and birth weight were evaluated by analysis of variance using PROC GLM of SAS (1999). Differences were determined using Fisher's protected LSD test (Steel et al., 1997). Significance was declared at $P < 0.05$. Trends were noted if $P < 0.10$.

Finally, Pearson correlation coefficients were calculated to evaluate relationships among colostral IGF-I, serum IGF-I at 0 and 48 h, the difference between 0 h and 48 h serum IGF-I concentration, body weight at birth, IgG levels at 48 h, total serum protein at 0 and 48 h, and serum GGT concentration at 0 and 48 h. Total serum protein concentrations at 0 and 48 h, and serum IgG concentrations at 48 h were obtained from Kirkpatrick et al. (2001).

Results

Linear regression of serum IGF-I at 48 h and colostral IGF-I revealed a significant positive relationship ($P < 0.05$) (Figure 1). The slope and intercept were 2.18 and 0.12, respectively. However, simple linear regression of colostral IGF-I and the difference in 48 h and 0 h IGF-I serum concentration did not show a relationship ($P > 0.25$) (Figure 2). Similarly, simple linear regression of colostral IGF-I and serum IGF-I at 0 h did not show a relationship ($P > 0.25$, $r^2 = 0.096$)

When treatment groups were divided according to pre-suckle serum IGF-I concentration, there was a significant ($P < 0.05$) time by group interaction. Although Group 1 (i.e., calves with initial serum concentrations of IGF-I < 10 ng/ml), had lower ($P < 0.01$) serum IGF-I concentrations than Group 2 (i.e., calves with initial serum concentrations of IG-I > 10 ng/ml) at 0 h, there were no significant differences ($P > 0.25$) in serum IGF-I concentrations between groups at 48 h (Figure 3). In Group 1, serum IGF-I concentrations did not change ($P< 0.10$) between 0 and 48 h, whereas in Group 2, serum IGF-I concentrations decreased ($P < 0.05$).

Sex did not affect ($P >0.25$) serum IGF-I concentration at 0 or 48 h (Table 1). Sex of the calf affected ($P < 0.01$) birth weight with males had greater ($P < 0.05$) birth weight than female calves (Table 1). Serum IGF-I at 0 and 48 h, as well as serum IgG at 48 h, total serum protein at 0 and 48 h, and serum GGT at 0 and 48 h were not affected ($P > 0.10$) by the sex of the calf.

Pearson correlation coefficients are in Table 2. Colostral IGF-I levels were positively correlated ($P < 0.05$) with serum IGF-I at 48 h, whereas serum IgG at 48 h was

positively correlated ($P < 0.001$) with total serum protein at 48 h. Serum GGT at 0 h was positively correlated ($P < 0.05$) with total serum protein at 0 h. There was a negative correlation ($P < 0.001$) between serum IGF-I at 0 h and the difference between 0 and 48 h serum IGF-I.

Discussion

Results of the present study revealed a significant positive relationship between colostral IGF-I concentrations and serum concentrations of IGF-I 48 h after birth. Consistent with these results, feeding colostrum at birth results in a higher level of circulating IGF-I than in calves fed mature cow milk (Grutter and Blum, 1991). Calves fed milk replacer plus rhIGF-I had greater plasma IGF-I concentrations than those fed either colostrum or milk replacer alone(Skaar et al., 1994). Vacher et al. (1995) catheterized the jejunum and the mesenteric vein draining the jejunum in newborn calves and detected [^{125}I]IGF-I in the mesenteric vein of these calves after its administration, however, the absorption time of [^{125}I]IGF-I was short. Other components of colostrum such as IGFBPs, not found in milk replacer, may reduce the absorption or stimulating abilities of colostral IGF-I (Baumrucker and Blum, 1994). Vacher et al. (1995) lowered the pH of colostrum to below 5 to allow the release of IGF-I from its binding proteins and found no increase in IGF-I absorption suggesting that factors other than IGFBPs in colostrum may influence the absorption of IGF-I. Lents et al. (1998) found that beef calves that had nursed exhibited decreased plasma IGF-I concentrations when compared

to those which had not nursed. Plasma IGF-I concentrations in these beef calves remained constant between d 1 and 4 post-calving (Lents et al., 1994). Within 24 h of birth, a neonate's intestine appears to be selectively hyperpermeable to large molecules (Gardner, 1984). Furthermore, intestinal absorption of polypeptides has been demonstrated in neonatal rats (Thornburg et al., 1987). Thus, IGF-I should be absorbable by the gut within the first 24 h of life whether it is bound by IGFBP or not. Our study shows that there are dramatic differences in serum IGF-I concentrations in neonates at birth. With such large variation in initial serum IGF-I concentration, it may be difficult to detect the contribution of colostral IGF-I to serum IGF-I concentrations in bovine neonates.

IGF-I orally administered to neonates stimulates gastrointestinal mucosal growth, numbers of IGF receptors in the intestinal mucosa, brush-border enzyme activity in 7-d old calves (Baumrucker et al., 1994a), increases the active ion transport in 5-d old pigs (Alexander and Carey, 1999), and increases enzyme activity in the jejunum in 14-d old rats (Young et al., 1990) and newborn rat pups (Ma and Xu, 1997). In addition, calves fed colostrum for six feedings have increased villus height compared with calves fed colostrum one time or those fed only milk replacer (Buhler et al., 1998). Similarly, systemic administration of IGF-I significantly increased the mucosal thickness in rat pups (Steeb et al., 1997). Collectively, these studies indicate that orally injested IGF-I stimulates changes in small intestinal villus size and function in several species of neonates including calves. Whether endogenous IGF-I found in colostrum acts in this manner is not clear.

While our study provides indirect evidence for absorption of IGF-I from the colostrum into the systemic circulation, the negative correlation between serum IGF-I at 0 h and the difference between serum IGF-I at 0 h and 48 h suggests that calves born with a high serum IGF-I will experience a greater decrease in serum IGF-I between birth and 48 h of life than calves born with low serum IGF-I. This latter observation is further supported by the finding that calves with greater IGF-I at birth (i. e., Group 2) had a significant decrease in serum IGF-I concentration between birth and 48 h compared to calves born with low serum IGF-I (i.e., Group 1) that had no significant change in serum IGF-I during the same interval (Figure 3). These results indicate that the concentration of serum IGF-I that a calf is born with is a more important contributor to 48 h serum IGF-I levels than is the amount of IGF-I consumed from colostrum. Recently, Hammon et al, (2000) reported that plasma levels of IGF-I decrease between 0 and 48 h after birth and that these IGF-I levels during the first 24 h of life are significantly influenced by how soon after birth the first colostrum is fed. Because birth weight was not significantly correlated with serum IGF-I at either 0 or 48 h, it is unlikely that birth weight accounts for differences in serum IGF-I levels among bovine neonates.

Plasma protein levels have been shown to increase with the consumption of colostrum (Rauprich et al., 2000), and results from the present study are consistent with this finding. The present study also indicated a significant positive relationship between total serum protein and GGT at 0 h and thus endogenous GGT may have contributed to the normal homeostatic levels of serum protein in the calf before colostrum feeding. The significant positive correlation between serum IgG at 48 h and total serum protein at 48 h suggests that IgG derived from ingestion of colostrum contributes significantly to serum

protein levels in neonatal calves. However, the accuracy of using total serum protein to detect Ig absorption has been questioned due to the interference of the hydration of the calf (Perino et al., 1993; Parish et al., 1997). Total serum protein includes both the immunoglobulin as well as the nonimmunoglobulin serum proteins (Parish et al., 1997). Because total serum protein concentrations can be affected by dehydration, other plasma constituents such as glucose, urea, and creatinine may contribute to the refractive index (Perino et al., 1993). Parish et al. (1997) and Perino et al. (1993) both determined that serum GGT level is a more useful test for passive transfer of colostral immunoglobulins than total protein due to the lack of influence of hydration. Calves are born with low to negligible GGT activity, and thus the bulk of neonatal serum GGT is colostral derived (Parish et al., 1997). This latter statement is supported by Hammon and Blum (1998) who found GGT activity significantly increased after colostrum intake. Similarly, serum GGT levels of calves in the present study increased between 0 and 48 h. The negative correlation between the birth weight and GGT levels at 48 h is likely due to the fact that the calves in this study were fed a constant volume of colostrum. Since GGT is colostral derived (Parish et al., 1997), this negative correlation verifies that larger calves received less colostrum on a per BW basis than smaller calves. Serum GGT, total serum protein, and serum IgG levels have been correlated in other studies (Perino et al., 1993), but not in the present study. These discrepancies may be due to the fact that blood samples were taken at 48 h in the present study while Perino et al. (1993) collected blood samples at 24 h, and Hammon and Blum (1998) collected blood at 1, 2, 4, and 7 h after feeding colostrum. Concentrations of GGT peak within 4 h after its oral ingestion and remain constant through 32 h, and slowly decrease during the subsequent 8 d (Baumrucker et al.,

1994b). Thus in the present study, blood samples may have been collected after the decline in serum GGT had already begun. Because total serum protein and GGT concentrations increased between 0 and 48 h, we can conclude that our calves received an appreciable amount of colostrum even though serum protein and GGT at 48 h were not correlated.

In the present study sex of the calves had a significant effect on birth weight of the calf with male calves weighing 16.7 % more than female calves. Similarly, Kertz et al. (1997) found male calves were 8.5% heavier than females. However, our study shows a lack of sex effect on serum IGF-I concentration in neonatal calves. A previous study (Davis et al., 1995) in 263 d old beef cattle found highly significant effects due to the sex of the calf on serum IGF-I concentration with males having higher IGF-I than females. Also, serum IGF-I concentrations were greater in male than female pigs at 84 d of age (Lamberson et al., 1995; Clapper et al., 2000), and in sheep at approximately 112 d of age (Roberts et al., 1990). There may be no sex effects shown in the present study due to the age of the animals. As an animal matures, so does the amount of steroids produced by that animal. Clapper et al. (2000) found that there was no difference in the serum IGF-I concentrations between boars, gilts, and barrows until 70 d of age. In addition to the increase in IGF-I seen at 84 d, there was also an increase in estradiol 17-β in which the boars exceeded the gilts and barrows (Clapper et al., 2000). In addition, there was an increase in the concentration of testosterone in males and a corresponding decrease in IGFBP-2. Ross et al. (1989) found IGFBP-2 to limit protein breakdown, thus if IGFBP-2 is limited due to testosterone more IGF-I could be available for growth resulting in a heavier weights in males (Clapper et al., 2000). Therefore, the age of the animal has a

significant impact on the amount of steroids in the circulatory system, making it likely that neonates would not be old enough to exhibit a sex effect on IGF-I concentration at 48 h post-calving.

No significant correlation between birth weight and serum IGF-I concentration was found in the present study. In contrast, Breier et al. (1988) found a significant correlation between IGF-I concentration and birth weight ($r = 0.78$, $n = 15$) in newborn male Friesian calves. In addition, Holland et al. (1997) found fetal body weight to be strongly correlated with serum IGF-I concentrations. These differences could be attributed to the fact that Breier et al. (1988) used strictly male Friesian calves, and Holland et al. (1997) used cross-bred beef calves. The impact of breed type and nutritional status of the dam on neonatal IGF-I levels at birth will require further study.

Conclusion

Results of the present study provide indirect evidence for absorption of IGF-I from colostrum into systemic circulation via a positive relationship between colostral IGF-I and serum IGF-I concentration at 48 h. However, there was also a negative correlation between serum IGF-I and the difference between serum IGF-I at 0 h and 48 h, suggesting that calves born with higher initial serum IGF-I concentration will experience a greater decrease in serum IGF-I between birth and 48 h of life. Further research is needed to determine the effects of other milk components and initial serum IGF-I on the transfer of IGF-I from colostrum to the neonate, as well as determine factors that may influence the rate of IGF-I decline in the neonate.

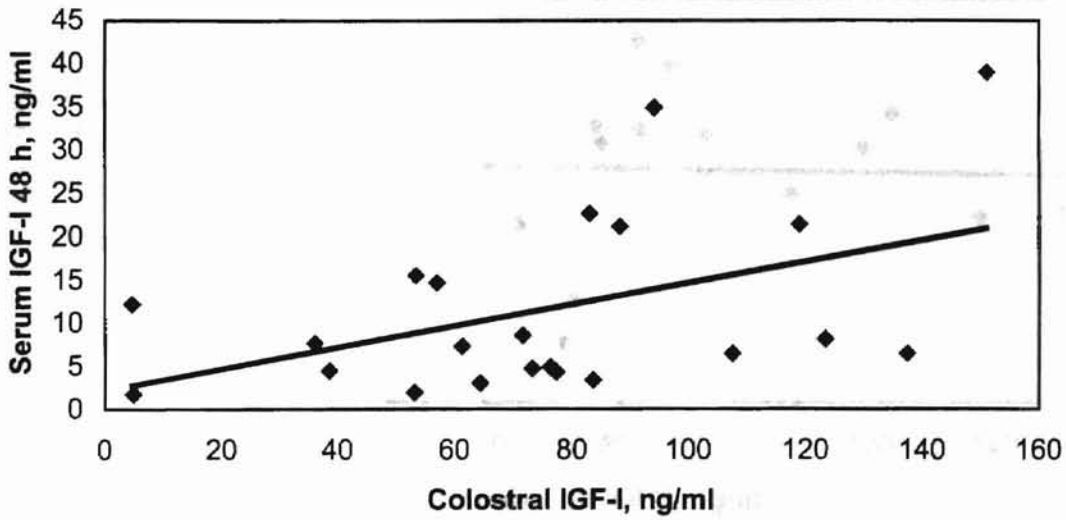

Figure 1. Linear regression for concentrations of serum IGF-I at 48 h and colostral IGF-I in all calves; $y = 2.18x + 0.12$, $r^2 = 0.204$, $P < 0.05$.

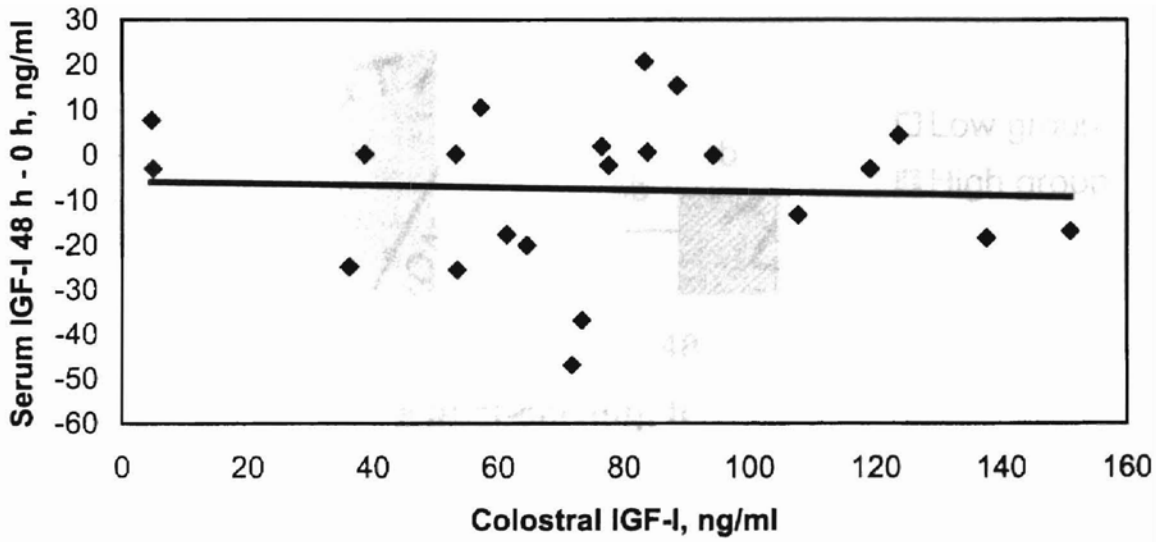

Figure 2. Linear regression for the difference in serum IGF-I concentrations at 48 h and 0 h and initial colostral IGF-I; $y = -5.89x + -0.02$, $r^2 = 0.003$, $P > 0.25$.

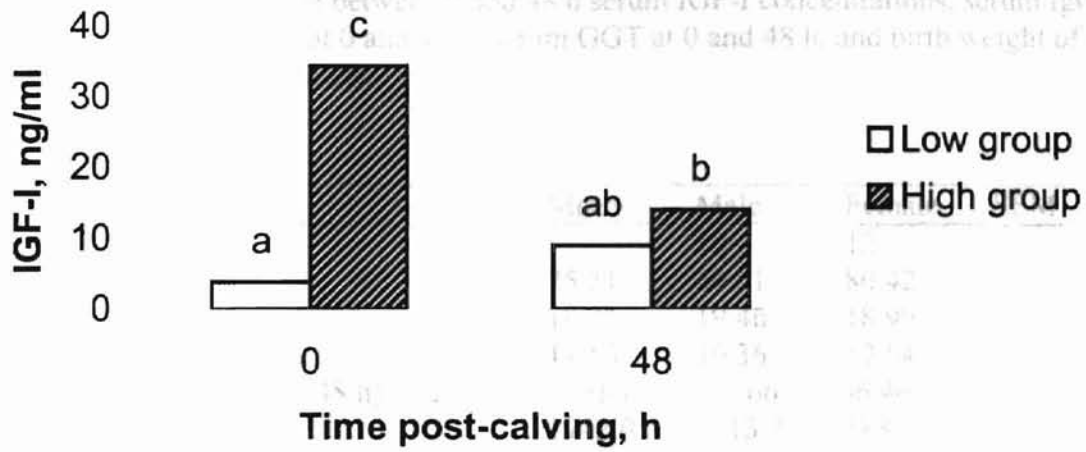

Figure 3. Serum IGF-I concentrations at 0 and 48 h for calves in the low group (0 h IGF-I < 10 ng/ml) and high group (0 h IGF-I > 11 ng/ml).
[ab]means without a common superscript differ ($P < 0.05$)
[bc]means without a common superscript differ ($P < 0.001$)

Table 1. Average colostral IGF-I concentration, serum concentrations of IGF-I at 0 and 48 h post-calving, difference between 0 and 48 h serum IGF-I concentrations, serum IgG at 48 h, total serum protein at 0 and 48 h, serum GGT at 0 and 48 h, and birth weight of male and female Holstein calves.

Variable	Mean	Male	Female	SEM
No. of Calves		10	12	
Colostral IGF-I*, ng/ml	75.51	69.61	80.42	11.58
Serum IGF-I at 0 h, ng/ml	19.21	19.46	18.99	5.569
Serum IGF-I at 48 h, ng/ml	11.55	10.36	12.54	3.201
Serum IGF-I Change (0 h – 48 h), ng/ml	-7.663	-9.106	-6.461	5.213
Serum IgG at 48 h, ng/ml	1942.0	2013.7	1882.7	292.6
Body weight at birth**, kg	38.93	42.23	36.17	4.506
Total Serum Protein at 0 h, g/dl	4.445	4.600	4.317	0.132
Total Serum Protein at 48 h, g/dl	6.068	6.150	6.000	0.240
Serum GGT at 0 h, U/L	24.67	23.78	25.33	3.665
Serum GGT at 48 h, U/L	1233.0	1079.3	1361.2	249.1

*Mean concentration of IGF-I in colostrum at first and second feeding.
** Male vs. female, $P < 0.05$.

Table 2. Correlation coefficients among concentrations of IGF-I in colostrum (Colo) and serum at 0 h and 48 h, the difference in serum IGF-I at 48 h and 0 h, serum IgG concentrations at 48 h, BW at birth, total serum protein concentrations at 0 and 48 h, and serum GGT concentrations at 0 and 48 h in Holstein calves (n = 22).

	0 h IGF-I	48 h IGF-I	Diff 48-0 h	IgG	BW	Protein 0 h	Protein 48 h	GGT 0 h	GGT 48 h
Colo	0.310	0.452*	0.131	0.131	-0.106	-0.0009	0.161	0.179	0.306
0 h IGF-I	.....	0.391	-0.824**	0.083	0.225	-0.224	0.007	0.154	-0.022
48 h IGF-I		.....	0.199	-0.330	-0.009	0.010	0.103	0.196	-0.283
Diff 48-0 h			.....	-0.291	-0.246	0.168	-0.259	-0.201	-0.151
IgG				.....	0.115	-0.092	0.880**	0.263	0.190
BW					.....	0.009	0.103	0.196	-0.604*
Protein 0 h						.....	0.043	0.573*	0.335
Protein 48 h							.....	0.347	0.203

*P < 0.05
** P < 0.001

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CHAPTER IV

Conclusion

Previous studies have shown an increase of IGF-I in the systemic blood after calves have been fed colostrum or milk replacer supplemented with rhIGF-I as opposed to those fed only milk replacer or mature cows milk. It has been shown in several species that this increase in IGF-I results in the stimulation of the small intestine increasing enzyme activity, villus height, and crypt depth. In the calf there have been conflicting studies as to the transfer of IGF-I from colostrum to the systemic blood and the effect of IGF-I if and when it is absorbed.

The results of this study provide indirect evidence for absorption of IGF-I from colostrum into systemic circulation. The present study showed a relationship between the colostral IGF-I concentration and the serum IGF-I concentration at 48 h. However, there was also a negative correlation between serum IGF-I and the difference between serum IGF-I at 0 h and 48 h, suggesting those calves born with higher initial serum IGF-I concentration will experience a greater decrease in serum IGF-I between birth and 48 h of life. Neither sex of calf nor its body weight were associated with serum IGF-I concentrations. The wide range of concentrations of serum IGF-I at 0 h and the rapid decline between 0 and 48 h could make determining the transfer of IGF-I from colostrum to the neonate difficult. To aid in experimental procedures, further investigation is needed to determine the causes for variation in blood levels of IGF-I and rate of decline

of IGF-I in the neonate. In addition, the role of the various components of colostrum on colostral IGF-I absorption needs further study.

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