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Colostrogenesis: Mass transfer of immunoglobulin G_1 into colostrum

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ABSTRACT

Bovine IgG_1 is thought to be specifically transported by a process of transcytosis across the mammary epithelial cells during colostrogenesis. Mammary IgG_1 appearance in cow colostrum has typically been reported as a concentration and shows IgG_1 concentration to be extremely variable because of animal variation, colostrum milking time, and water dilution effects. To identify animal IgG_1 transfer capacity and separate it from the other effects, our objective was to determine first colostrum IgG_1 total mass. We collected 214 samples of totally milked first colostrum with recorded colostrum weights from 11 Pennsylvania dairy farms that participated in Pennsylvania Dairy Herd Improvement Association, analyzed colostrum for IgG_1 by ELISA, and calculated total IgG_1 mass. Median and mean concentrations of IgG_1 were 29.4 mg/mL and 37.5 ± 30.2 mg/mL, respectively, with a range of 9 to 166 mg/mL. However, total mass of IgG_1 had a median of 209.1 g, mean of 291.6 ± 315.8 g, and a range of 14 to 2,223 g. Colostrum IgG_1 concentration showed no relationship with colostrum volume, but IgG_1 mass had a positive relationship with volume. Colostrum IgG_1 mass was related to IgG_1 concentration ($R^2 = 0.58$). Using DHIA records for 196 animals, we established milk production for these animals to a 15-d equivalent. An established milk secretion relationship to mammary parenchyma tissue (secretory tissue) was calculated and showed no relationship of IgG_1 mass with mammary parenchyma tissue. In addition, we show that approximately 10% of the sampled animals had IgG_1 mass greater than 1 standard deviation above the mean (high mass transfer) and represented all parities tested (1–7). Whereas first-lactation animals showed less overall calculated parenchyma tissue when compared with other parities, approximately 10% of the first-lactation group animals were capable of high mass transfer, with one transporting 2,029 g into first colostrum. Concentration variance of IgG_1 can be attributed to water inclusion, whereas mass transfer provides a clear indication of animal IgG_1 transfer capacity. The specific mechanism of bovine mammary IgG_1 transfer is not clear, but secretory tissue mass does not explain the variation observed. We hypothesize that the animal variation is attributable to endocrine regulation or genetic variation of the transporter(s).

Key words: lactation, mammary, colostrogenesis, colostrum

INTRODUCTION

The success of commercial dairies depends on a reliable supply of replacement heifer calves with good potential for milk production. Although calf management practices have evolved over the years to reduce calf morbidity and mortality, the current level of neonatal calf disease remains at 9% of preweaned heifers (USDA, 2002). Calf diarrhea (scours) and other digestive diseases accounted for >62% of all preweaned heifer mortality.

Maternal passive transfer of immunity in neonates varies among species, specifically with the IgG antibodies (Butler, 1974). In cattle, transfer of IgG_1 to the neonate is accomplished solely by the ingestion of colostrum because in utero transfer does not occur. The mammary transport of Ig into colostrum is very specific, concentrating IgG_1 but not IgG_2 (Larson et al., 1980). Immunoglobulin G_1 is thought to be transported across mammary epithelial cells by the Fc receptor of the neonate (bFcRn) by a process termed transcytosis (Ghetie and Ward, 2000) and in the calf intestinal tract by passive transfer (Weaver et al., 2000).

The concentrations of IgG_1 and IgG_2 in serum (approximately equal at ~10–12 mg/mL), colostrum, and milk indicate very selective transfer of IgG_1 accounting for a 10-fold enhancement in colostrum concentration followed by a similar decrease in mature milk, both relative to serum concentrations (Sordillo et al., 1987). It is important to note that this concentration effect does not occur with IgG_2. Studies have shown a large variation in the concentration of IgG_1 in first milked colostrum. A recent study by Kehoe et al. (2007) showed a wide range of 10 to 79 mg/mL, with an average of 39.5 mg/mL in first colostrum collected from 58 Pennsylvania dairy farms. Part of this variation has been attributed to the timing of milking of the colostrum,

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because copious quantities of milk components appear en masse with delayed milking following parturition. Osmotic molecules such as lactose begin to incorporate more water that has a diluting effect on IgG_1 concentration. Thus, such water inclusion induces potential variation in each animal colostrum sample but would not be expected to affect colostrum total mass of IgG_1. The literature provides no information concerning the possible reabsorption of IgG_1 into the mammary cell once it has been secreted.

Thus, total mass of IgG_1 transferred by a mammary gland would be independent of water influx and more useful in establishing animal variation in transport capacity and perhaps transport mechanisms that are present during dairy cow colostrogenesis. We hypothesized that differential mass transfer could be associated with 1) a set amount of transcytosis capacity per mammary cell and more or less cells; 2) differential expression of the transcytosis capacity per cell; or 3) differential expression of transcytosis variants that have different capacities to move serum IgG_1 to mammary secretions.

The objective of this study was to establish the animal variation of IgG_1 mass transfer associated with first milked colostrum and compare these findings with IgG_1 concentration, estimates of mammary secretory tissue mass, and other available information in an attempt to answer hypothesis 1 above.

MATERIALS AND METHODS

Collection of Colostrum

The Pennsylvania State University Institutional Animal Care and Use Committee approval number 28889 was obtained for colostrum sample collection. We asked 11 commercial dairy farms in Pennsylvania to collect all of the colostrum from the first milking and record colostrum weights. A 50-mL tube was provided for the colostrum sample, animal identification, and colostrum weight. Colostrum was frozen by farm personnel until sample pick-up dates that never exceeded 4 wk. The frozen colostrum was allowed to thaw at refrigeration temperatures and a subsample of the collected volume was centrifuged at $3{,}500 \times g$ for 15 min at ambient temperature. The surface fat was removed by aspiration and the remaining supernate above any pellet was collected and frozen at −20°C until analysis.

Milk Yield at 15 d and Calculation of Parenchyma Tissue

Test-day milk weights (n = 196) were obtained from DHIA. Herds were enrolled in monthly milk testing with first test-days generally occurring between calving and 30 d, so records were standardized to the midpoint of that interval. Weights were analyzed with a model that included fixed parity number, herd-test-date, and random milk yield curve effects specific to each cow. Solutions were used to estimate milk yield on d 15 of lactation for all cows. The correlation between d 15 estimate of yield and the nearest test-day yield was 0.98. For lactating goats, it has been determined that approximately 1.0 g of parenchyma tissue is needed to produce 1.9 mL of milk/d (Linzell, 1966). This estimate is supported by more recent studies with dairy cows (Dewhurst et al., 1993; Knight and Dewhurst, 1994; Magaña-Seville and Sandoval-Castro, 2003). Parenchyma tissue is a measure of secretory cells in the mammary gland that provide the volume of milk.

Analysis of IgG_1

Samples were analyzed by an ELISA specific for bovine IgG_1 (Bethyl Laboratories Inc., Montgomery, TX; catalog no. E10–116). The capture antibody was prepared at a 1:100 dilution in a total volume of 100 μL for each well. Unknown samples were serial diluted and initially 2 duplicates each of 2 dilutions (5×10^{-5} and 5×10^{-6}) were tested for assay range sensitivity and correlation. After establishment, we found that a 5×10^{-5} dilution factor was best for most samples, although some samples that had very low or very high IgG_1 concentration required repeats at different dilutions. A Microtek microtiter plate (Hsinchu, Taiwan) read horseradish peroxidase (Bethyl Laboratories Inc.) reduction of tetramethyl benzidene (TMB, Rockland Immunochemicals Inc., Gilbertsville, PA) at 450 nm after final incubation for 10 min at ambient temperature. Inter- and intraassay coefficients of variation were 9.26 and 3.73%, respectively.

pH Analysis of the Colostrum Sample

After subsampling and centrifugation, the remaining refrigerated colostrum sample (~50 mL) was rapidly warmed to 37°C in a water bath and immediately tested for pH with a combination Phresh refillable flow-on-demand electrode (Beckman Coulter Inc., Fullerton, CA). This electrode provides a means to flush highly viscous or dirty samples such as colostrum from the junction after each measure to prevent clogging. Duplicate measures were conducted with frequent (after every 5 samples) restandardization of the electrode to ensure accuracy.

Determination of Colostrum Lactose

Samples were selected to represent average pH (n = 10) and low pH (n = 5) to measure lactose content of

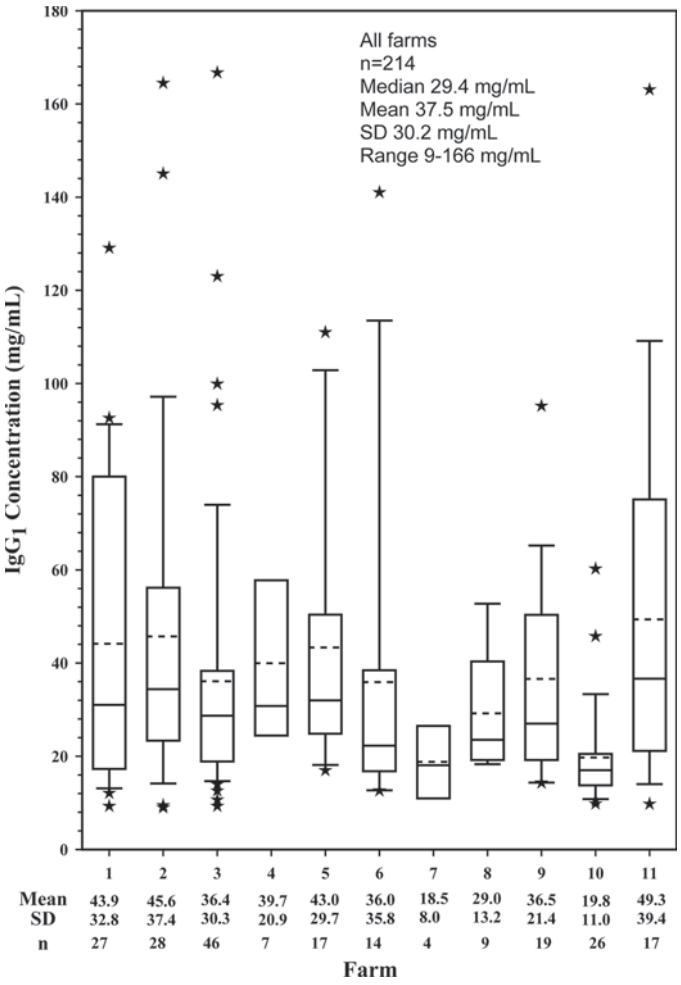

Figure 1. Immunoglobulin G_1 concentration in first milked colostrum. Data are a box plot from 11 Pennsylvania dairy farms and represent 214 colostrum samples. Analysis was by ELISA. Data are the median (—), mean (. . .), and whisker (error) bars that represent 10th and 90th percentiles, with individual cow concentrations plotted (star shape) when they fall below the 10th and above the 90th percentiles. The x-axis shows farm mean, standard deviation, and animal number.

the colostrum. Lactose was analyzed using a Lactose Assay Kit (K624–100, BioVision, Mountain View, CA). Samples were assayed in duplicate after experimentation to determine appropriate dilutions of the centrifuged colostrum samples. Data were expressed as milligrams of lactose per milliliter of centrifuged sample.

Statistics

Data were plotted with Sigma Plot (Systat Software Inc., Chicago, IL) and linear regression was computed by least squares means and the coefficient of determination (R^2) was determined (Systat Software Inc.). Immunoglobulin G_1 relationships were determined using PROC CORR in SAS (SAS Institute, Cary, NC). When correlations had P-values <0.1, the variables were determined by PROC GLM in SAS.

RESULTS

Figure 1 shows the overall IgG_1 concentration median, mean, and standard deviation of the 214 collected samples. The figure also shows the farm, sample number, farm IgG_1 means, and standard deviations and the variation plot. The overall median and mean for all farms and animals were 29.4 and 37.5 mg/mL, respectively, with a range of 9 to 166 mg/mL. Fourteen animals had concentrations above the 90th percentile, whereas 13 had concentrations below the 10th percentile. The median concentration being lower than the mean indicates that most farms have some high IgG_1 transfer animals that increase the mean.

Figure 2 shows the overall IgG_1 mass median, mean, and standard deviation of the 214 collected samples. The figure also shows the farm, sample number, farm IgG_1 mass, and standard deviation and the variation plot (10th and 90th percentiles; error bars) of IgG_1 mass from the individual farm samples. The overall median and mean for all farm and animal IgG_1 mass were 209.1 and 291.6 g, respectively, with a range of 14 to 2,223 g. Fourteen animals had a mass above the 90th percentile and 14 had a mass below the 10th percentile. The lower median mass value for each farm again shows that most farms have animals that transfer high quantities of IgG_1 mass and serve to increase the mean.

Figure 3 compares both IgG_1 concentration and mass to colostrum volume. Figure 3A shows that there is no significant correlation of IgG_1 concentration with colostrum volume ($P = 0.65$), whereas Figure 3B indicates a mass versus volume relationship ($R^2 = 0.234$; $P < 0.0001$).

Figure 4 shows that total colostrum IgG_1 mass is related to colostrum concentration ($R^2 = 0.58$; $P < 0.0001$). Arrows on the y-axis indicate the mean of 291 g and where plus 1 standard deviation would occur (606 g), above which we considered to be high IgG_1 mass transfer. High mass transfer animals (n = 14) represented 6.5% of the animals tested. All farms except 2 had at least 1 high mass transfer animal. Farms 7 and 8 likely did not show this type of animal because few animals were sampled (n = 4 and 9, respectively).

Figure 5 shows no relationship ($R^2 = 0.01$; $P = 0.62$) of total colostrum mass of IgG_1 when plotted against calculated parenchyma tissue mass for 196 animals. Parenchyma tissue mass was calculated from DHIA production records as described in Materials and Methods.

Figure 6 shows that among first-lactation cows, which had generally less calculated parenchyma tissue

than high parity animals, there were 4 animals that we considered to be high mass transfer animals. All parities tested (1–7) had some animals that fell into the high transfer capacity category.

Figure 7 shows no relationship of colostrum pH when compared with total colostrum IgG_1 mass ($P = 0.92$). Surprisingly, the average pH of colostrum measured at 37°C was 6.03 ± 0.33, with a range of 4.85 to 6.85. Low pH has been attributed to fermentation of lactose and fatty acids (Polzin et al., 1977). Because we depended upon the participating farms to quickly freeze the colostrum samples after collection, we wished to test for lactose in a subset of average and low pH colostrum samples. If colostrum samples had remained at warmer temperatures for an extended period of time, fermentation would reduce the lactose content. Lactose concentration in the 15 analyzed colostrum samples averaged 1.2 ± 0.5 mg/mL. The 10 (pH 6.16 ± 0.09) samples representing average pH had a lactose concentration of 1.0 ± 0.457 mg/mL, whereas the 5 (pH 5.22 ± 0.133) samples representing low pH had a lactose concentration of 1.578 ± 0.448 mg/mL.

DISCUSSION

The classes of Ig in ruminants are generally the same as in other mammalian species. Their concentrations in serum, colostrum, and milk have been documented to indicate very selective transfer of IgG_1, accounting for a 10-fold enhancement in colostrum followed by an equivalent decrease in mature milk relative to serum concentrations (Sordillo et al., 1987). It is important to note that this concentration effect does not occur with IgG_2 (Butler, 1974; Sasaki et al., 1976; Larson et al., 1980). Whereas concentration indicates the specific transport of IgG_1, it does not provide information concerning the mass transfer capacity of the process. This latter concept is important because at the time of colostrum delivery (first milking) after parturition, the mammary gland is already in transition to mature milk production. This process appears to end the selective IgG_1 transfer to colostrum and the induction of copious quantities of milk components and has been described as the transition between lactogenesis I (secretory differentiation: colostrum formation) and lactogenesis II (secretory activation: beginning of copious milk secretion; Nguyen and Neville, 1998). Among mature milk components, lactose (milk sugar) is the major osmole, but small ions also appear to contribute (Ontsouka et al., 2003). Thus, around the time of parturition and thereafter, milk lactose is rapidly added to the secretion while tight junctions form to retain the lactose (Nguyen and Neville, 1998), resulting in the inclusion of more water. Water increases colostrum volume and decreases

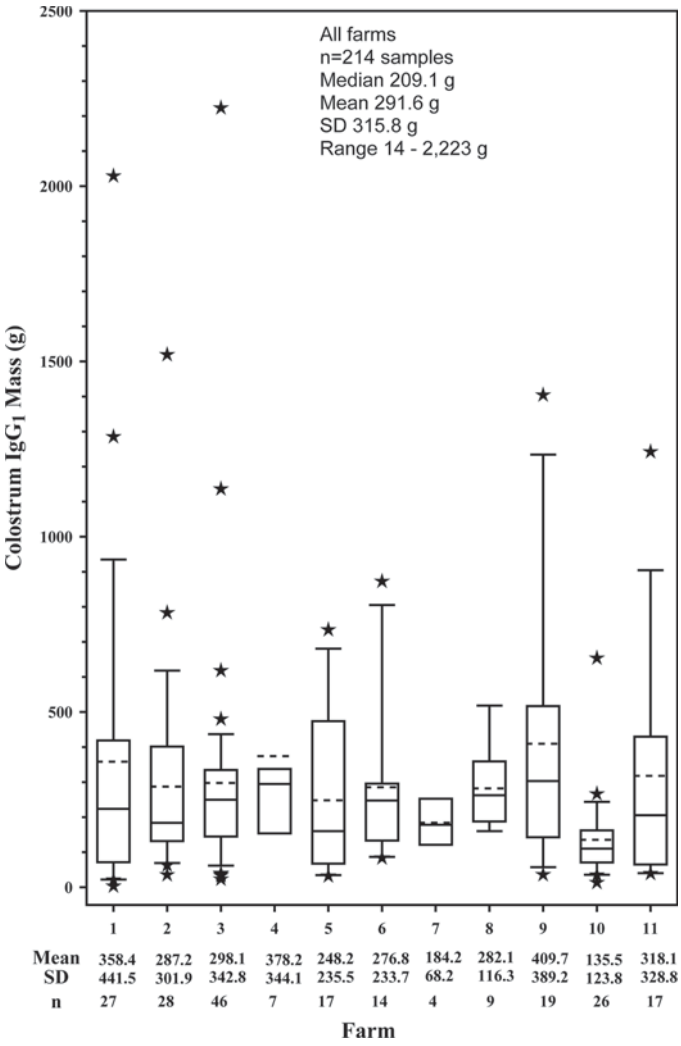

Figure 2. Immunoglobulin G_1 mass in first milked colostrum. Data are a box plot from 11 Pennsylvania dairy farms and represent 214 colostrum samples. Analysis was by ELISA. Data are the median (—), mean (. . .), and whisker (error) bars that represent 10th and 90th percentiles, with individual cow concentrations plotted (star shape) when they fall below the 10th and above the 90th percentiles. The x-axis shows farm mean, standard deviation, and animal number. Mass was calculated from first colostrum volume and IgG_1 concentration shown in Figure 1.

colostrum component concentrations. Thus, secretory activation variation in each animal and the timing of colostrum removal (on-farm milking) following parturition contributes to colostrum concentration variation but should not affect colostrum mass of IgG_1. We show that total mass of IgG_1 transferred by a cow mammary gland establishes the animal IgG_1 transfer capacity during colostrogenesis.

Interestingly, Figure 3 showed no significant relationship when we plotted IgG_1 concentrations against colostrum volume, yet a relationship was observed when IgG_1 mass was plotted against volume. This clearly is a reflection of the water dilution effect that occurs with

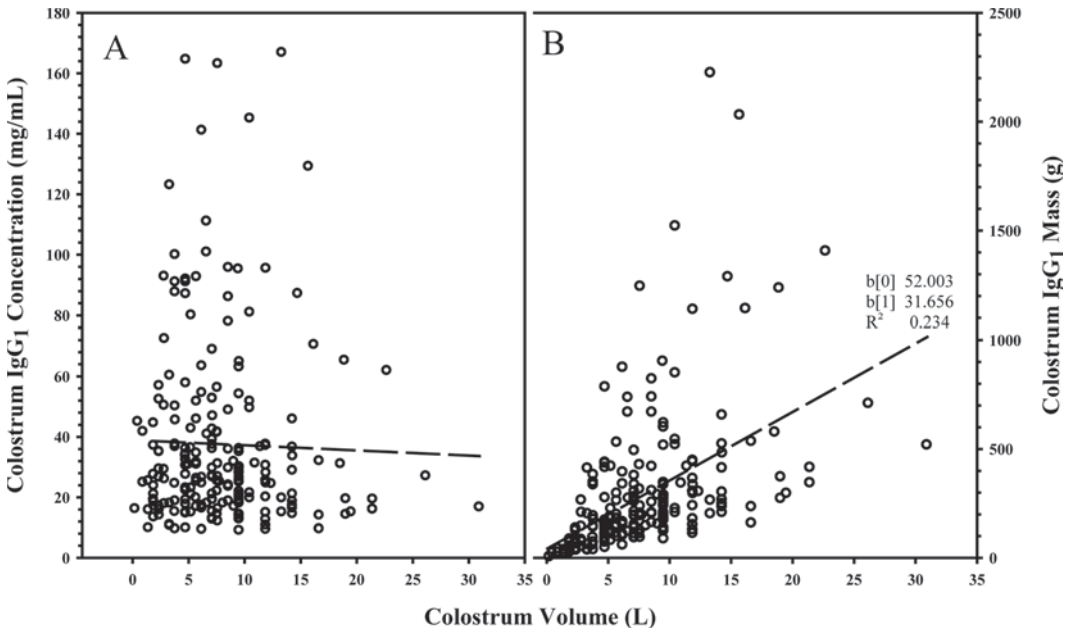

Figure 3. Relationships of immunoglobulin G_1 A) concentration and B) mass to colostrum volume. Lines on figures indicate linear relationship ($R^2 = 0.234$; $P < 0.0001$).

a concentration calculation; total mass is not affected by this parameter. Nevertheless, volume explains only a part of mass transfer. Plotting IgG_1 mass against IgG_1 concentration clearly shows a strong relationship ($R^2 = 0.58$), indicating that animals that can concentrate more IgG_1 in their colostrum will likely have greater mass.

The mean IgG_1 concentration in our study of 214 colostrum samples was 37.5 ± 30.2 mg/mL. This finding is generally in agreement with other reports ranging from 48.2 ± 28.9 mg/mL (Pritchett et al., 1991) to a recent report of 39.5 ± 12.2 mg/mL (Kehoe et al., 2007). Our findings showed a wide variance with almost all farms having some cows with very low and high IgG_1 colostrum concentrations. Although it is clear that colostrum phase mammary cells have leaky tight junctions (Nguyen and Neville, 1998; Stelwagen et al., 1998), the selectivity for IgG_1, high mass, and high concentration obtained by some animals cannot be explained by leakiness. Tight junction leakiness would not allow concentrations above that of the blood and would not exclude IgG_2 from colostrum. Research indicates that nutrition does not affect colostrum IgG content (Halliday et al., 1978), so the capacity to transfer high IgG_1 concentrations into colostrum must be dependent upon mechanisms in the mammary gland.

The main objective of this study was to determine total mass transfer of IgG_1 in dairy cows. Our analysis revealed a mean IgG_1 mass of 291.6 ± 315.8 g for the 214 colostrum samples collected from Pennsylvania dairy farms. The reported concentration variance for colostrum IgG_1 (Pritchett et al., 1991; Kehoe et al., 2007) is likely attributable, in part, to the inclusion of water resulting in lower values. Mammary secretory parenchyma tissue mass is related to the capacity to produce milk volume during lactation. Generally, the quantity of tissue is reflected by the amount of DNA (cells) in the mammary gland during lactation (Miller et al., 2006). During the prepartum colostrum phase, fewer mammary cells would be expected to be present when compared with the secretory cells present during peak lactation (Capuco et al., 2003; Annen et al., 2007). We extrapolated available DHIA milk production records to obtain milk production at d 15 of lactation to place each animal at an equal stage of lactation. Although it is clear that d 15 parenchyma tissue would be greater than that observed any time during the colostrum phase, we assumed that this early period of lactation would be representative of the tissue mass present during colostrogenesis. Using the d 15 parenchyma tissue calculations, we showed that there is no relationship ($R^2 = 0.01$; $P = 0.608$) between IgG_1 mass and d 15 parenchyma tissue mass. These data indicate that more mammary secretory tissue mass (secretory cells), although providing more milk during lactation, does not equate to transcytosis of more IgG_1 into colostrum. This may be explained by the fact that milk secretion encompasses many mechanisms for components and pathways of secretion whereas transcytosis of IgG_1 during colostrogenesis is clearly more focused (less pathways) and perhaps more flexible for regulation.

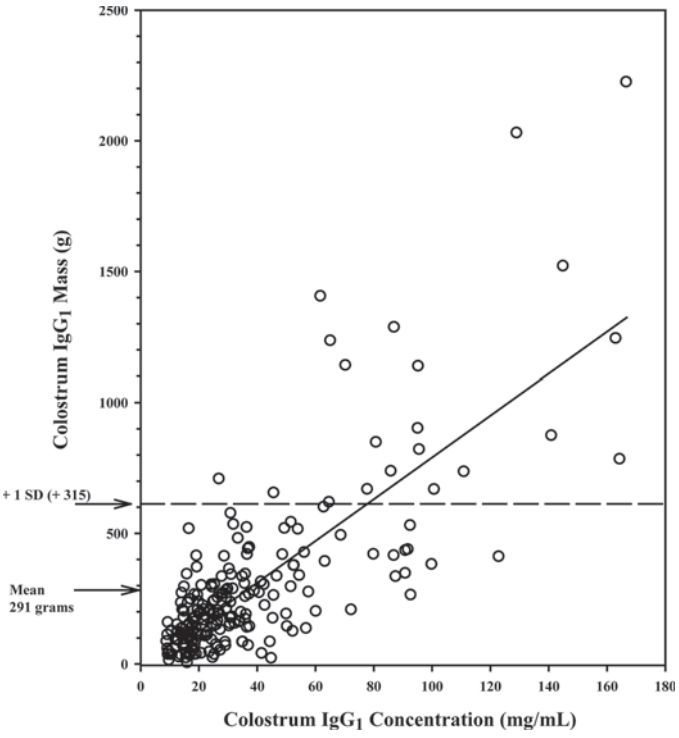

Figure 4. Immunoglobulin G_1 mass relationship with IgG_1 concentration in colostrum. Broken line shows where +1 SD occurs; solid line is linear relationship ($R^2 = 0.58$; $P < 0.0001$).

Colostrum pH values of 6.2 and 6.32 have been was reported by McIntyre et al. (1952), Nonnecke and Smith (1984), and Foley and Otterby (1978). Whereas freezing colostrum does not alter the composition or pH (Carlson and Muller, 1977), fermentation of colostrum decreases the pH. Polzin et al. (1977) attributed this decrease to VFA production and not to changes in lactic acid. We asked the 11 participating farmers to quickly freeze the colostrum samples for our later pick-up; however, we had no control over the timing of this process. All samples were obtained frozen from the farms. Our analysis of the lactose content of selected average pH and low pH colostrum samples did not indicate that the low pH colostrum samples had been subjected to fermentation.

Failure of passive transfer of IgG_1 is strongly associated with increased calf mortality caused by infectious disease (McGuire et al., 1976). The industry has set a guideline of feeding high quality colostrum (>50 mg/mL of IgG) within the first hours of birth in attempt to reach a calf serum IgG concentration of ≥13.4 mg/mL (Tyler et al., 1996, 1999). There are 2 specific reasons for this concentration and timing. First, there is a colostrum concentration problem partially caused by delayed first milking. However, we show a mass problem that is not likely affected by water inclusion, suggesting an IgG_1 transcyctosis problem. Cow colostrum shows extremely high animal-to-animal variation in IgG_1 mass (14–2,223 g). The hypothesized causes of this variation are endocrine (Casey and Plaut, 2007) and genetic (Doleschall et al., 2005; Mayer et al., 2005).

Studies have been conducted in vivo and in vitro in an attempt to understand the initiation and termination of colostrogenesis. The process has been reported to be detected at 2 wk prepartum (Brandon et al., 1971) when circulating 17β-estradiol is increasing and progesterone is decreasing (Convey, 1974; Tucker, 1979, 1981). The artificial induction of lactation clearly establishes 17β-estradiol and progesterone as critical components of this initiation (Smith et al., 1971; Smith and Schanbacher, 1973; Willett et al., 1976; Barrington et al., 2000).

Studies conducted around the time of parturition have indicated that both prolactin (Barrington et al., 1999) and glucocorticoids (Brandon et al., 1971; Winger et al., 1995), part of the lactogenic complex (Tucker, 1979, 1981), appear to inhibit the colostrogenesis process and

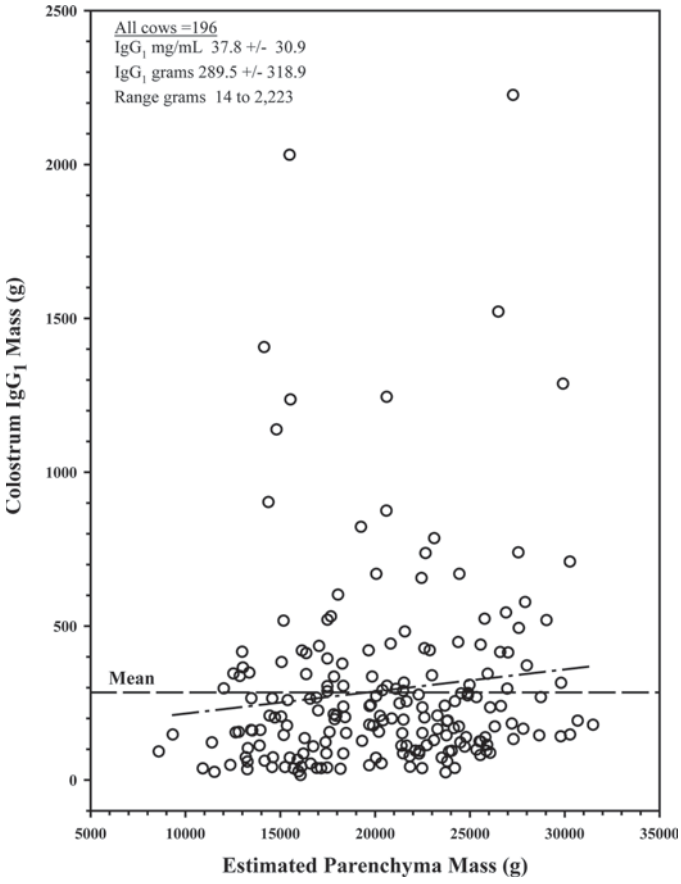

Figure 5. Immunoglobulin G_1 mass relationship with calculated mammary parenchyma tissue mass. Broken line shows mass mean; broken-dotted line is linear relationship. Parenchyma mass was estimated for d 15 of lactation from DHIA records. (Broken-dotted line: $R^2 = 0.01$; $P = 0.62$.)

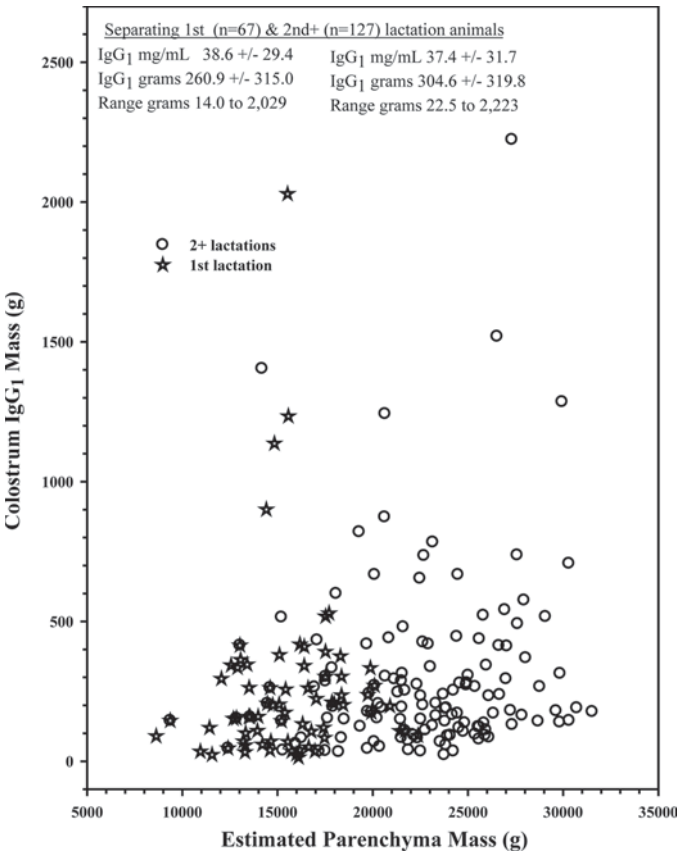

Figure 6. Immunoglobulin G_1 colostrum mass of first lactation contrasted within greater parities when plotted against calculated mammary parenchyma tissue mass. Star shapes are 67 colostrums from animals in lactation 1; open circles are 127 colostrums from animals in lactation $\geq$2. Parenchyma mass was estimated for d 15 of lactation from DHIA records.

induce copious milk production. It is important to note that the proposed IgG_1 transporter (bFcRn), when expressed in mammary tissue of lactating mice, has been reported to only recycle IgG_1 (Cianga et al., 1999; Lu et al., 2007) and not conduct epithelial transfer by transcytosis (appearance in rodent milk). Thus, some doubt about bFcRn role in bovine IgG_1 transcytosis during colostrum formation has been suggested (Cervenak and Kacskovics, 2009). However, because endocrine regulation of the bFcRn may control the transcytosis/recycling mechanisms and the testing was conducted during lactation (Lu et al., 2007), the capacity of the bFcRn to conduct transcytosis was not adequately tested with the transgenic mice.

CONCLUSIONS

We show that the mass transfer of IgG_1 during colostrogenesis is variable and is a better descriptor of IgG_1 biological transfer that is not influenced by water inclusion. The lack of IgG_1 mass relationship with the mass of parenchyma tissue indicates that mass transfer is not dependent on the amount of mammary gland secretory tissue. That all lactation parities, including first lactation, have animals with high capacity to transfer IgG_1 mass supports this finding. That bovine colostrum pH is low in first milked colostrum is difficult to reconcile with established mechanistic criteria of IgG_1 transcytosis by the bFcRn receptor. However, the timing of IgG_1 transfer to colostrum has not been established and the mass may be transcytosed early in colostrogenesis when colostrum pH is more neutral. Nevertheless, whatever mechanism of transfer occurs, some cows have enormous differential capacity to transfer IgG_1 mass during colostrogenesis that has health effects on the bovine neonate.

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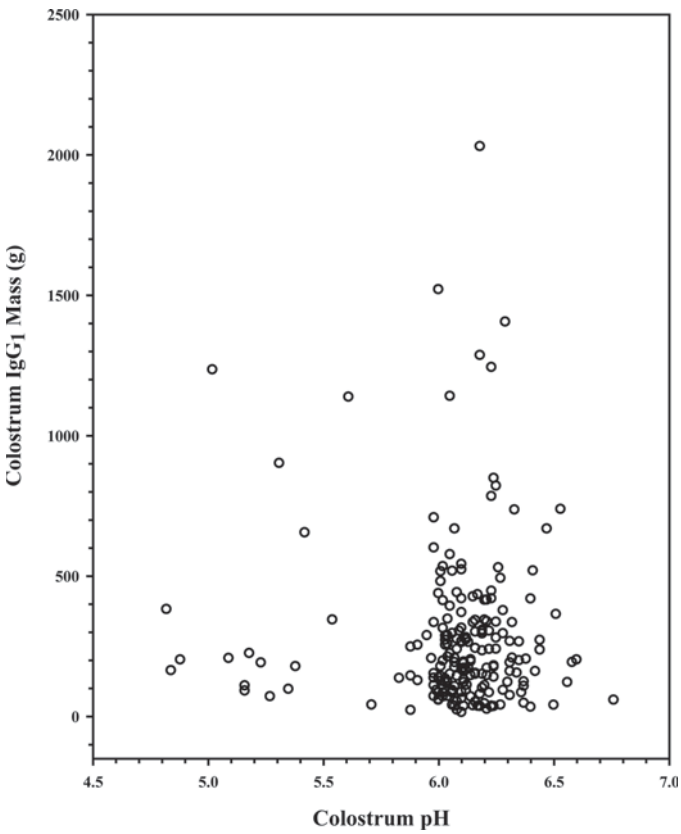

Figure 7. Immunoglobulin G_1 mass relationship with colostrum pH. Data are measured pH at 37°C for individual colostrum samples. Mean was 6.03 ± 0.33.

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