Mammary immunoglobulin transfer rates following prepartum milking

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ABSTRACT

Colostrum formation is thought to occur slowly over an extended period (4 wk) prepartum. Furthermore, colostrum formation is highly variable among cows in total volume, IgG₁ concentration, and mass obtained at first postpartum milking. Recent work has suggested that a rapid transfer of IgG₁ to secretions may occur if animals are milked prepartum. Our objective was to establish the concentration, mass, and mass transfer rates of IgG₁ in multiparous Holstein cows ($n = 11$, parity = 3.6 ± 1.1) milked prepartum (-74 to -1 h) and again around 4 h postpartum. Blood concentrations of IgG₁ were very low (<1 mg/mL) in 7 cows at prepartum milking and did not decline following prepartum milking. Cows showed variability in the capacity to recover total volume, IgG₁ concentration, and IgG₁ mass. Three groupings of cows were considered based on the time between the 2 milkings (prepartum + 4 h postpartum): long-time (-74 to -54 h, $n = 3$), medium-time (-25 to -17 h, $n = 4$), and short-time (< -13 h, $n = 4$) groups. The average rates of transfer of these groups were 1.4 ± 0.8 , 3.0 ± 1.3 , and 25.1 ± 15.8 g/h, respectively. The data indicate that a longer time between prepartum and postpartum milking is not a main factor in IgG₁ secretion transfer. Furthermore, because blood concentrations did not change after prepartum milking and the mass of blood plasma IgG₁ was not sufficient to account for the mass occurring in postpartum colostrum, a source of IgG₁ other than blood circulation appears to be present during colostrogenesis.

Key words: colostrum, immunoglobulin, mammary, transfer rates

INTRODUCTION

Colostrum immunoglobulins provide passive immunization to the newborn. The importance of adequate passive transfer for minimizing morbidity and mortality has been demonstrated (Quigley and Drewry, 1998;

Weaver et al., 2000). Concentrations of IgG₁ and IgG₂ in the serum of dairy cows are approximately equal, at ~ 10 to 20 mg/mL (Butler, 1974; Guidry et al., 1980), but selective mammary transfer of IgG₁ accounts for up to a ~ 10 -fold enhancement (Sordillo et al., 1987) in colostrum.

However, cow colostrum has extremely high animal-to-animal variation in IgG₁ concentration (11.8 to 74.2 mg/mL; Kehoe et al., 2007; Morrill et al., 2012) and mass (30 g to >2 kg; Baumrucker et al., 2010). Current explanations of this variation include endocrine effects (Casey and Plaut, 2007) and genetics (Doleschall et al., 2005; Mayer et al., 2005). Changes in serum prolactin and progesterone have little effect on colostrum IgG₁ concentration near parturition (Gross et al., 2014). Lactation number, breed of cow, length of the dry period (Pritchett et al., 1991; Tomkins and Jaster, 1991; Mansfeld et al., 2012), and method of analysis (Li-Chan and Kummer, 1997; Gelsinger et al., 2015) may also contribute to colostrum variation.

Colostrogenesis takes place mainly in the weeks before parturition, and the secreted product has high concentrations of IgG₁ (Butler, 1986). Selective IgG₁ transfer from blood to secretions occurs ~ 3 wk before parturition (Brandon et al., 1971), as evidenced by ^{125}I -labeled blood IgG₁ appearing in the secretions (Sasaki et al., 1976). Sasaki et al. (1977) also showed a modest plasma IgG₁ decline from 14 to ~ 5 mg/mL and indicated that IgG₁ half-life (5.5 ± 1.7 d) decreased (4.1 d) after parturition. However, this finding disagrees with current concepts of IgG₁ decline, as well as the more recently reported half-life of >20 d (Murphy et al., 2014) that is likely the result of recycling through the neonatal Fc receptor (FcRn) system (Kacskovics et al., 2006). Throughout the lifetime, FcRn internalizes and recycles IgG₁ in many tissues (Baker et al., 2009; Giragossian et al., 2013).

Based on declining concentrations of blood IgG₁, colostrum formation is thought to begin 3 to 4 wk before parturition (Brandon et al., 1971). However, individual cows might start colostrogenesis at different times prepartum. Relative to specific IgG₁ transfer mechanisms, we have hypothesized that a slow rate of transfer from blood to mammary secretions, coupled with variable

Received April 27, 2016.

Accepted July 8, 2016.

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lengths of the colostrogenesis period among animals, contribute to this variation (Baumrucker and Bruckmaier, 2014). Recent evidence suggests that colostrum formation starts earlier than 4 wk prepartum (Chandra et al., 2013). Mammary secretion IgG₁ concentrations were significantly higher than blood concentrations within 8 d (Winger et al., 1995; Stark et al., 2015) after the start of an induced lactation protocol similar to that used by (Macrina et al., 2011) with nonpregnant dairy cows. Initiation of colostrogenesis may be important, because different animals may start the process at different times, and if the process is slow, animals with an earlier start may gain much higher concentrations and mass, accounting for some of the documented animal variation (Baumrucker et al., 2014a). A difference in colostrogenesis start time may be related to circulating concentrations of steroids, differential sensitivity of their receptors in the mammary glands, or both, but recent work has shown little, if any, effect of progesterone decline on the end of colostrogenesis and the start of lactogenesis (Gross et al., 2014).

In a preliminary experiment, we separately milked the mammary gland quarters of a pregnant dairy cow ~26 h before parturition and again 4 h after parturition. We found that IgG₁ mass from the quarters was ~100% recovered at 4 h postpartum (total of ~30 h; Baumrucker and Bruckmaier, 2014), suggesting that transfer of IgG₁ can be very fast. In a recent study of pregnant cows with a standard dry period, we extended the data to show that IgG₁ transcytosis can be a rapid process in the mammary glands of some animals after prepartum milking, with some interesting changes in composition (Gross et al., 2014). Milking prepartum (–74 to –1 h) produced an average IgG₁ concentration that was equivalent to that of control animals milked postpartum. In prepartum-milked cows, the overall mass of IgG₁ was independent of the time between the 2 milkings, and IgG₁ mass was not different between the 2 milkings. Total colostrum mass was similar for prepartum-milked (sum of 2 milkings) and control animals (1 milking) (Gross et al., 2014). These findings showed that the transcytosis mechanism of IgG₁ can be very fast but extremely variable between animals. The objectives of the current study were (1) to critically examine the animal-to-animal variation in IgG₁ transfer from blood to mammary gland secretions obtained from dairy cows milked once before parturition and again after parturition; and (2) to define the blood plasma concentration decline and mammary appearance and establish IgG₁ transfer rates into the first milked postpartum colostrum. We hypothesized that prepartum milking would induce an increased flux of IgG₁ from blood to mammary secretions that would appear as a blood concentration decline and recovery.

MATERIALS AND METHODS

Animals and Experimental Procedures

The experiment was conducted in accordance with the guidelines of Swiss law on animal production and approved by the Veterinary Office of the Canton Fribourg, Switzerland (permit no. 2011–40-FR). The study included 11 multiparous Holstein dairy cows (parity 3.6 ± 1.1) that were milked before parturition in the same season of 2012 and were part of a larger group of animals that has been reported (Gross et al., 2014). One cow from the previously reported group (Gross et al., 2014) was excluded due to missing samples. In the present study, our goal was to milk cows at approximately 24 h before estimated parturition to maximize secretion volume for the calf, and then again 4 h after calving. The actual prepartum milking (C1) occurred from –74 to –1 h before calving; the second milking (C2) occurred at 4.6 ± 0.3 h postpartum. Prepartum and postpartum milking colostrum mass was recorded, and proportional samples were frozen at –20°C until analysis. Starting at 4 d before expected parturition, blood samples were taken from the jugular vein 3 times daily at 0600, 1400, and 2200 h until calving, and 1 additional sample was collected shortly before postpartum milking. Blood samples were collected in 9-mL evacuated tubes coated with EDTA and kept on wet ice until centrifugation at $2,500 \times g$ for 15 min at 4°C to harvest plasma. Plasma was subsequently stored at –20°C until analysis. Animal blood volume was calculated assuming 55 mL/kg of BW (Reynolds, 1953), and plasma volume was assumed to be 55% of blood volume.

Milk and Plasma Sample Analysis

Colostrum IgG₁ concentration was determined using a modified ELISA (Bovine IgG₁ ELISA Quantitation Set; Cat. No. E10-118; Bethyl Laboratories Inc., Montgomery, TX), as described previously (Baumrucker et al., 2014a). Blood IgG₁ and IgG₂ were determined using kits E10-118 and E10-117, respectively. Results were expressed as IgG concentration in milligrams per milliliter or total grams (mass).

Statistical Analysis

Data were analyzed using the CORR and MIXED procedures in SAS (version 9.2; SAS, Institute, Inc., Cary, NC). The CORR procedure determined the linear relationship between the C1 and C2 variables; the MIXED procedure evaluated IgG₁ = IgG₂ cow time and cow $\times$ time interaction or IgG₂ = IgG₁ cow time and cow $\times$ time interaction.

RESULTS

Prepartum milking (C1) occurred from -0.9 to -73.7 h (24.7 ± 7.1 h) before parturition. The second milking (C2) was conducted at 4.6 ± 0.3 h postpartum. Five cows showed a decline in plasma IgG₁ concentration occurring during the 4 d before parturition, and the other 6 showed very low concentrations with no change (0.40 ± 0.08 mg/mL; Figure 1). Seven cows exhibited very low blood concentrations of IgG₁ (0.29 ± 0.16 mg/mL) in the last 48 h before parturition. Cows did not reveal a decline in plasma IgG₁ because of prepartum colostrum milking.

Average plasma IgG₁ was different between cows ($P < 0.001$) and changed with time ($P < 0.01$); we observed a time $\times$ cow interaction ($P < 0.001$). Average plasma IgG₂ concentration (Figures 2, 3, and 4) was different due to 3 cows (1607, 1646, and 1763; $P <$

0.001). Analysis using the CORR procedure between the 2 milkings of all cows indicated that colostrum IgG₁ concentration and mass were positively correlated (>0.9 ; $P < 0.001$). Colostrum total mass (kg = yield) at the second milking was negatively related to mass at the first milking (-0.61 ; $P = 0.049$).

Because the prepartum milking occurred at different times, we blocked the animals into 3 separate groups based on the time between the prepartum and the postpartum colostrum milkings. The grouping became the long-time group (Figure 2; < -74 to -54 h, $n = 3$); the medium-time group (Figure 3; < -25 to -17 h, $n = 4$); and the short-time group (Figure 4; < 13 h, $n = 4$), relative to parturition.

Two of 3 long-time cows had very low blood IgG₁ concentrations during the sampling period (Figure 2; < 1 mg/mL). In addition, 2 of the 3 recovered approximately 16.5% of the colostrum mass (Figure 2 inset);

Figure 1. Prepartum milking does not affect plasma IgG₁ concentration around parturition. Arrows indicate the prepartum milking time for each cow.

the other cow recovered the equivalent initial colostrum mass (C1) in the postpartum (C2) milking. Two of the cows did not recover the original C1 IgG₁ concentration, but the other long-time cow did (cow 1607; Figure 2, A). None of the cows recovered the C1 IgG₁ mass (Figure 2, B) despite the long time between the 2 milkings (>54 h). The IgG₁ mass transfer rate for this group averaged 1.42 ± 0.8 g/h.

All medium-time cows had low blood IgG₁ concentrations (Figure 3; <1.6 mg/mL) at the time of prepartum

milking (C1). In addition, 2 of the 4 cows recovered more than the original colostrum mass (inset); the other 2 cows did not recover the initial C1 colostrum mass. All of the cows approached recovery of the original C1 IgG₁ concentration (Figure 3, A), but this was low for the range of typical colostrum concentration of 35 to 40 mg/mL (Baumrucker et al., 2010). Two cows recovered equivalent IgG₁ mass (Figure 3, B) in spite of the shorter time (<25 h) between milkings. The mass transfer rate for this group averaged 3.0 ± 1.3 g/h.

Figure 2. Prepartum (C1) and postpartum (C2) milking of colostrum in the long-time cow group (long interval between 2 milkings). The large line graph shows the plasma concentration of individual cows for IgG₁ (●) and IgG₂ (□). The small bar graph inset shows the colostrum total mass (kg) at the 2 times of collection (C1 vs. C2). Graphs A and B show the concentration (A, mg/mL) and total mass (B, g) of IgG₁ in the collected colostrum (C1 vs. C2). Graph B also shows the mass transfer rate of IgG₁ from the C1 to the C2 collection.

Figure 3. Prepartum (C1) and postpartum (C2) milking of colostrum in the medium-time cow group (medium interval between 2 milkings). The large line graph shows the plasma concentration of individual cows for IgG₁ (●) and IgG₂ (□). The small bar graph inset shows the colostrum total mass (kg) at the 2 times of collection (C1 vs. C2). Graphs A and B show the concentration (A, mg/mL) and total mass (B, g) of IgG₁ in the collected colostrum (C1 vs. C2). Graph B also shows the mass transfer rate of IgG₁ from the C1 to the C2 collection.

Figure 4. Prepartum (C1) and postpartum (C2) milking of colostrum in the short-time cow group (short interval between 2 milkings). The large line graph shows the plasma concentration of individual cows for IgG₁ (●) and IgG₂ (□). The small bar graph inset shows the colostrum total mass (kg) at the 2 times of collection (C1 vs. C2). Graphs A and B show the concentration (A, mg/mL) and total mass (B, g) of IgG₁ in the collected colostrum (C1 vs. C2). Graph B also shows the mass transfer rate of IgG₁ from the C1 to the C2 collection.

Cows in the short-time group exhibited a range of blood IgG₁ concentrations (<1 to <2.8 mg/mL) at the time of prepartum milking (C1) that was higher than that of the other groups (*P* < 0.05). In addition, 3 cows recovered equivalent or greater C2 colostrum mass compared with the original colostrum C1 mass (inset). The mass transfer rate for this group averaged 25.1 ± 15.8 g/h.

We calculated the mass of IgG₁ in plasma at prepartum milking (C1) and compared it with IgG₁ mass in colostrum at the postpartum milking (C2; Table 1). The C2 colostrum IgG₁ mass generally showed an average of 7.4 ± 5.7 times greater mass over the available mass in the plasma pool at the time of the C1 milking (Table 1). We know that immunoglobulins are replaced by plasma cells (Butler, 1974) and clearly would explain the results of the long-time cows and perhaps even the medium-time cows, but it is notable that cows 1698 (short time) and 1725 (medium time) showed an IgG₁ mass in colostrum that was >11- and 18-fold higher, respectively, than that of the plasma pool. Furthermore, we detected no change in plasma IgG₁. The other 3 short-time cows exhibited 3.4-, 4.3-, and 6.0-fold higher IgG₁ in C2 colostrum compared with plasma mass in shorter times (<10 h) and without any change in plasma concentration (Figure 1).

DISCUSSION

Plasma IgG₁ concentrations in our study, measured in the 4 d before parturition, were low and had likely already declined from expected pre-colostrogenesis values of 10 to 20 mg/mL (Butler, 1974; Guidry et al., 1980). Our data generally support reports of blood declines starting earlier than our 4-d prepartum period (Brandon et al., 1971). Surprisingly, plasma concentrations of

IgG₁ for most animals were extremely low (<1 mg/mL) as parturition approached (~24 h prepartum). This was different from literature values of 9 to 10 mg/mL occurring near to parturition using radial immune-diffusion procedures (Sasaki et al., 1976). Analysis techniques could explain some of these differences (Gelsinger et al., 2015).

Interestingly, the blood plasma concentration did not change as a result of the 1 prepartum milking of the mammary glands of pregnant dairy cows. Continuous milking without a dry period results in IgG₁ accumulation in milkings during the last week before parturition, and the concentration varies among cows (Baumrucker et al., 2014b). We had hypothesized that the concentration would decline and subsequently recover as a result of the prepartum milking; this was clearly not true. However, IgG₁ was transferred to new mammary secretions without any detected effect on plasma concentrations. It could be argued that the concentration was so low (<1 mg/mL) that no effect could be detected. However, the total mass transfer shown (Table 1) indicated that the plasma source, if totally used, would account for <30% for most cows (n which was not likely to be accounted for by release from plasma cells).

The 3 figures illustrating individual cow data showed great variation in the capacity to recover colostrum mass, IgG₁ concentration, and IgG₁ mass. The transfer rates of long-time cows were biased by the many hours taken to accomplish the transfer (>54 h). The medium-time animals showed higher transfer rates than the long-time cows and better recovery of the colostrum mass, suggesting that the mechanisms involved in this process increase as parturition approaches. The most interesting results were those from the short-time animals. The transfer rates (g/h) were very fast and supported the concept of increasing capacity for colostrum formation

Table 1. Comparison of IgG₁ concentration and calculated mass in plasma at prepartum milking and colostrum IgG₁ mass at postpartum milking¹

Cow no.	Time milked (h prepartum)	Plasma (mg/mL)	Plasma (g)	Colostrum (g)	Colostrum: blood fold ratio ²
1783	−1	1.65	35.0	120	3.4
1677	−2	1.26	26.1	161	6.2
1665	−6	0.6	12.3	54	4.4
1698	−9	2.44	48.9	573	11.7
1630	−13	0.45	8.9	48	5.4
1748	−14	0.41	8.7	29	3.3
1646	−14	0.67	13.2	55	4.2
1725	−21	0.21	4.3	80	18.8
1607	−50	3.03	60.0	106	1.8
1763	−70	0.31	6.2	38	6.1
1695	−71	0.39	8.2	135	16.6
Mean ± SD					7.4 ± 5.7

¹All cows were milked postpartum at 4.6 ± 0.3 h.
²Fold ratio is the colostrum IgG₁ mass divided by the plasma mass.

as parturition nears. In general, the shorter the time between the prepartum and postpartum milkings, the higher the transfer rate. These findings supported the rejection of our hypothesis that IgG₁ transfer is slow and that cows with a longer colostrogenesis period would provide more IgG₁ mass. Clearly, IgG₁ transfer rates are variable, and more time between the 2 milkings did not result in greater IgG₁ transfer.

The main question that arises from these findings is: how can the gland transfer 24 to 44 g/h without a decline in blood IgG₁ concentrations? It must be that another unaccounted pool of IgG₁ is readily available for transfer to the secretions. It is interesting that the 4 animals in the short-time group generally had higher IgG₁ concentration (>25 mg/mL) in the C2 milking than the medium-time group. The short-time animals also generally recovered the colostrum mass in the time between milkings. This would likely be influenced by a mass transfer of IgG₁ that exerts high osmotic pressure (Yousef et al., 1998) and facilitates the recovery of colostrum volume. However, we do not know if the transfer rate accelerates in cows that are not milked prepartum. It is likely that prepartum milking would have an accelerating effect on IgG₁ transport related to the concentration effect on biological transport mechanisms (Christensen, 1975). However, we did not observe this in the long-time group.

The timing of the decline in blood plasma IgG₁ concentrations and the capacity to transfer IgG₁ to secretions is highly variable between cows. We reject our working hypothesis that blood plasma concentrations would decline and recover with premilking. Furthermore, we cannot link the surprisingly low blood plasma concentrations and lack of any change in IgG₁ concentration to the rates of transfer we have shown. Finally, the capacity to transfer >44 g/h while the plasma pool appears to be unaffected indicates that another pool of IgG₁ is readily available to be moved into the secretions. We hypothesize that this source may be the mammary epithelial intracellular FcRn recycling pool or large amounts of plasma cells close to the mammary epithelial cell (Nickerson, 1989).

We know that FcRn recycling exists in many tissues (Roopenian and Akilesh, 2007; Giragossian et al., 2013) and is a component of mammary cells (Kacskovics, 2004). If mammary cell recycling is the source of IgG₁ transfer, then the reported decline in blood plasma IgG₁ that occurs ~4 wk before parturition (Brandon et al., 1971) may be the result of the induction of FcRn recycling in bovine mammary epithelial cells and not the direct result of IgG₁ transfer to luminal secretions. A plasma cell source of IgG₁ remains a viable explanation, but a decline in plasma cells occurs during involution

(Nickerson, 1989) and it is not known if this persists during colostrogenesis.

CONCLUSIONS

During a very narrow period in the last days immediately prepartum, mammary IgG₁ secretion appearance rates in milking cows were highly variable. Prepartum blood concentrations of IgG₁ were extremely low, and one-time prepartum milking of cows did not affect IgG₁ concentrations in the circulation. Nevertheless, IgG₁ appearance rates in secretions can be high and are apparently not affected by plasma IgG₁ concentration. Finally, blood IgG₁ mass does not account for the appearance of postpartum colostrum mass, strongly indicating an unknown pool of available IgG₁.

ACKNOWLEDGMENTS

We thank Zoetis (Florham Park, NJ) for the monetary gift that made portions of this research possible.

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