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Predictors of Low Milk Volume among Mothers Who Delivered Preterm

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Abstract

Background: Factors associated with successful provision of mother's own milk (MOM) for premature infants in a Japanese neonatal intensive care unit (NICU) context are not well known.

Objective: We determined the independent risk factors for low milk volume at day 4 postpartum and formula feeding at the time of NICU discharge.

Methods: We reviewed the medical records of mothers who delivered at < 32 weeks' gestation. We determined maternal, premature infant, and milk expression variables predictive of (1) day 4 postpartum milk volume being less than the cohort median and (2) formula feeding at the time of NICU discharge, reported as adjusted odds ratios (95% confidence interval).

Results: Among 85 dyads, median (quartile range) milk volume on day 4 postpartum was 153 (34-255) mL. The rate of formula feeding at discharge was 42%. Mothers delivering by cesarean (vs vaginal) delivery had 4.3-fold (1.5-12.4) greater odds of day 4 milk volume < median ($P < .01$). Pregnancy-induced hypertension, delayed milk expression initiation, and low pumping frequency were strongly associated with cesarean delivery. Subsequently, mothers with day 4 milk volume < median (vs ≥ median) had 7.1-fold (2.6-19.5) greater odds of formula feeding at discharge ($P < .01$).

Conclusion: Cesarean delivery is associated with lower milk volume on day 4 but may represent a composite of underlying risk factors for low milk volume in the early postpartum period. Further, low milk volume on day 4 is a strong correlate of lack of exclusive breast milk feeding at NICU discharge.

Keywords

breastfeeding, breast milk, cesarean delivery, lactation, preterm delivery

Well Established

Breast milk is the most important nutrition for premature babies, but mothers of premature infants have difficulty establishing and sustaining lactation.

Newly Expressed

Among Japanese mothers who delivered prematurely, we observed cesarean delivery to be a strong predictor of low milk volume on day 4; subsequently, low milk volume on day 4 predicted lack of exclusive breast milk feeding at discharge from the neonatal intensive care unit.

Background

Breast milk provides premature infants with superior nutrition, reduction in infections, improved gastrointestinal development, and improved neurodevelopmental outcomes.[1] A recent randomized controlled trial demonstrated lower incidence of surgical necrotizing enterocolitis and fewer days of parenteral nutrition in premature infants receiving human milk as compared to those receiving formula.[2] For these reasons, the provision of human milk is an important component of the premature infant care plan.

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Compared to mothers of term infants, mothers of premature infants have difficulty establishing and sustaining lactation.[3,4] Hill et al[3] reported that only 50% of mothers of premature infants were able to express sufficient milk to meet their infant's needs at 6 weeks postpartum.

Milk banks can augment insufficient supplies of mother's own milk (MOM). When factoring in the increased costs of donor milk and limitations on its use, the importance of optimizing early and sustained provision of MOM becomes apparent. However, the factors associated with optimizing the provision of MOM remain poorly characterized. Human milk feeding occurs under a unique set of circumstances in Japanese neonatal intensive care unit (NICU) settings. For example, hand expression is an effective technique for removal of colostrum[5] and is chosen at 71% of Japanese NICUs as the initial technique of breast expression.[6] Second, unless contraindicated, all Japanese mothers who deliver preterm initiate breast expression. This expectation is driven by Japan's high regard for human milk feeding of the premature infant combined with a traditional lack of human milk banks, with the first modern Japanese human milk bank being established in 2013. Moreover, Japanese mothers have low prevalence of diabetes mellitus (2%)[7] and obesity (body mass index [BMI] > 30) (3.5%).[8] Because of this unique set of circumstances, we decided to examine the risk factors for low milk supply among mothers of premature infants in a typical Japanese NICU setting.

The aims of this analysis are to characterize breast milk volume during the first 4 days postpartum and the provision of MOM at the time of NICU discharge, as well as to determine maternal, infant, and milk expression variables predictive of low milk volume on day 4 and formula feeding at the time of NICU discharge.

Methods

Study Design

A retrospective study of medical records from Showa University Hospital (Tokyo, Japan) was performed. We extracted medical record data for mother-infant dyads who delivered at < 32 weeks' gestation from January 2008 to December 2012. Of the 148 mother-infant dyads at < 32 weeks' gestation during the study time frame, 61 were excluded: (1) multiple birth (N = 16), (2) premature infants who died during hospitalization (N = 33), (3) premature infants who transferred from another hospital (N = 4), (4) premature infants not yet discharged at time of data collection (N = 3), (5) mother's obstetrician determined lactation to be contraindicated (N = 4), and (6) mothers who had a history of breast surgery (N = 1). Thus, 87 mother-infant dyads were included in the analytical cohort.

This study was approved by the Showa University Hospital Institutional Review Board.

Study Setting

At Showa University Hospital, midwives determine milk expression initiation time in accord with mothers' condition. Before the onset of copious milk production (ie, during stage I lactogenesis), mothers express breast milk exclusively by hand. The midwives consider the onset of copious milk production to occur when mothers feel breast fullness and/or milk coming and/or milk volume suddenly increasing. After the onset of copious milk production, mothers switch to double pumping with a hospital-grade electric breast pump (Medela, Inc, McHenry, Illinois, USA). Thus, hand and mechanical expression are used sequentially. Milk expression is recommended 6 or more times per day.

Showa University Hospital has 7 International Board Certified Lactation Consultants (IBCLCs), including 5 NICU physicians and 2 NICU nurses, but it does not have dedicated IBCLCs. Midwives mainly provide lactation support to mothers during the mothers' hospital stay, and the NICU staff mainly provides lactation support to mothers whose infants are admitted to our hospital NICU. When mothers have breastfeeding problems that staff cannot resolve, IBCLCs provide lactation support.

Upon discharge, mothers are advised to rent a hospital-grade electric breast pump. However, mothers may choose their own preferred expression technique and frequency after discharge.

Regardless of premature or term delivery, the discharge date (assuming the mother has no other complications) depends only on delivery mode. Mothers who deliver vaginally are usually discharged on day 6 postpartum. Mothers who deliver by cesarean are usually discharged on day 8 postpartum.

Study Variables

We extracted the following from the hospital medical record.

Maternal characteristics: maternal age, BMI, parity, gestational diabetes, pregnancy-induced hypertension (PIH), and delivery mode.
Premature infant characteristics: gestational age, birth weight, day of life upon discharge, and corrected age upon discharge.
Milk expression variables: milk expression initiation time (hours after delivery), expression frequency on days 1 through 4 postpartum, and milk volume on days 1 through 4 postpartum (or until maternal discharge from the hospital, up to day 8 postpartum).

We did not investigate milk expression variables after discharge. Forty percent of the mothers who delivered vaginally were discharged by day 5 postpartum. Thus, to reflect the characteristics of the full cohort, the data after day 5 postpartum were not used for statistical analysis.

Milk Volume Measurement

Milk volume is measured during the mother's hospital stay. If breast milk volume is low, breast milk is collected through hand expression and the milk is measured in a syringe to the nearest 0.1 mL. After the onset of copious milk production, breast milk is expressed by electric breast pump and then measured using a digital scale to the nearest 1 g (Tanita Corporation, Tokyo, Japan). We collected the milk volume data from the medical record.

Outcome Measures

We examined outcomes related to early and sustained provision of MOM. For the early provision of MOM, we defined *low milk volume on day 4* as being less than the cohort median. For the sustained provision of MOM, we used the outcome, *formula feeding at discharge*, which we defined as any infant fed formula as a supplement to MOM, or exclusively fed formula, 24 hours prior to discharge.

Of 87 mother-infant dyads who were included in the analytical cohort, 85 of them have complete data for low milk volume on day 4 (2 had missing data on this outcome) and 81 of them have complete data for formula feeding at discharge (6 were excluded for this outcome for the following reasons: transferred to another hospital before 36 weeks corrected age [N = 2], stopped lactation due to the need to initiate chemotherapy [N = 2], and infant diagnosed [after day 4 postpartum] with a condition where MOM is contraindicated [N = 2]).

Statistics

All quantitative variables were categorized as greater than or equal to versus less than the cohort median. The prevalence of our 2 outcome measures, low milk volume on day 4 and formula feeding at discharge, was examined according to maternal, premature infant, and milk expression variable categories. Chi-square analysis was used to determine significant associations.

Maternal, premature infant, and milk expression variables with chi-square P value < .10 for a given outcome measure were then further examined using multiple variable logistic regression. In the cases where the same variable was significant over a series of days, we selected the day on which the association was the strongest for multiple variable model development. We report the odds ratio (OR) and 95% confidence interval (CI) for both unadjusted and adjusted models.

All analyses were performed using Excel Statistics version 1.09 (SSRI Company, Ltd, Tokyo, Japan).

Results

Sample Characteristics

Characteristics of the cohort are shown in Table 1. Overall, 72% of the participants delivered by cesarean. Median (quartile range) maternal prepregnant BMI was 20 (19-22) kg/m^2. The Japan Society for the Study of Obesity defines BMI > 25.0 kg/m^2 as obese.[9] Based on this definition, 8% of study participants were obese. Only 2% of study participants had diabetes in pregnancy; thus, this factor was excluded from further analysis. The medians for gestational age and infant birth weight were 29.2 (27.6-30.6) weeks and 1125 (903-1309) grams, respectively.

Median (quartile range) milk expression initiation time was 20 (8-29) hours postpartum, with 36% of mothers initiating milk expression after 24 hours postpartum. Thus, median pumping frequency on day 1 postpartum was only 1 (0-3) time. By day 3 postpartum, median milk expression frequency reached the recommended 6 or more times per day.

Median (quartile range) milk volume on day 4 postpartum was 153 (34-255) mL. Median milk volumes on days 1 through 4 are shown in Figure 1, stratified by day 4 milk volume category. The group with high (greater than or equal to median) milk volume on day 4 postpartum consistently had a higher median milk volume from days 1 through 3 postpartum as compared to the group with low (less than median) milk volume on day 4 (Figure 1). Individual milk volume trajectories over the first 5 days postpartum are shown in Figure 2. The majority of mothers with high milk volume on day 4 exhibited a dramatic increase in milk volume between days 2 and 3 postpartum (solid lines in Figure 2). We did not assess the timing of stage II lactogenesis; however, Figure 2 suggests that most of the mothers with low milk volume on day 4 experienced delayed onset of stage II lactogenesis, which is defined as onset of copious milk production after 72 hours.[11]

Predictors of Low Milk Volume on Day 4

The unadjusted bivariate associations with low milk volume on day 4 postpartum and formula feeding upon discharge are shown in Table 1. Among maternal and premature infant characteristics, only older maternal age (P = .04) and cesarean delivery (P < .01) were at least marginally associated with low milk volume on day 4.

The milk expression variables that were at least marginally (P < .10) associated with low milk volume on day 4 postpartum were the following: lower pumping frequency and lower milk volume on days 1, 2, and 3. Among the milk expression variables, day 2 frequency was most strongly associated with day 4 milk volume (P = .02). Given the likelihood of a similar causal pathway for low milk volume on day 4 and low milk volumes on days 1, 2, and 3, these latter variables were not included in logistic regression analysis.

Logistic regression analyses of the independent predictors of low milk volume on day 4 are shown in Table 2. In a model that includes all 3 variables meeting entry criteria (maternal age, cesarean delivery, and pumping frequency on day 2), cesarean delivery and older maternal age remained

Table 1. Milk Volume Status at Day 4 and Breastfeeding Status at Discharge Stratified by Select Characteristics.

Characteristic[a]	No. per Stratum[b] (Day 4)	Day 4 Milk Volume < 153 mL (Median)		No. per Stratum[c] (Discharge)	Formula Feeding at Discharge	
		No. (%)	*P* Value		No. (%)	*P* Value
Total N	85	42 (49)		81	34 (42)	
Maternal						
Age, y			.04			.83
< 33	38	14 (37)		37	16 (43)	
≥ 33	47	28 (60)		44	18 (41)	
Body mass index, kg/m^2			.59			.72
< 20	43	20 (47)		41	18 (44)	
≥ 20	42	22 (52)		40	16 (40)	
Delivery mode			< .01			.41
Cesarean	61	36 (59)		58	26 (45)	
Vaginal	24	6 (25)		23	8 (35)	
Pregnancy-induced hypertension			.14			.94
Yes	15	10 (67)		14	6 (43)	
No	70	32 (46)		67	28 (42)	
Parity			.72			.79
Primiparous	51	27 (53)		49	20 (41)	
Multiparous	34	15 (44)		32	14 (44)	
Infant						
Gestational age, wk			.98			.75
< 29	36	18 (50)		35	14 (40)	
≥ 29	49	24 (49)		46	20 (43)	
Birth weight, g			.91			.92
< 1125	42	21 (50)		40	17 (43)	
≥ 1125	43	21 (49)		41	17 (41)	
Z-score at birth[d]			.45			.26
< –0.67	41	22 (54)		37	18 (49)	
≥ –0.67	44	20 (45)		44	16 (36)	
Day of life at discharge[e]			.23			.32
< 92	41	17 (41)		41	15 (37)	
≥ 92	42	23 (55)		40	19 (48)	
Corrected age at discharge, wk[e]			.70			.44
< 42	35	16 (46)		35	13 (37)	
≥ 42	48	24 (50)		46	21 (46)	
Milk expression						
Initiation time, h			.16			.05
< 20	41	17 (41)		39	12 (31)	
≥ 20	44	25 (57)		42	22 (52)	
Pumping frequency on day 1, No. times			.09			.08
0	29	18 (62)		27	15 (56)	
≥ 1	56	24 (43)		54	19 (35)	
Pumping frequency on day 2, No. times			.02			.70
< 4	30	20 (67)		29	13 (45)	
≥ 4	55	22 (40)		52	21 (40)	
Pumping frequency on day 3, No. times			.06			< .01
< 6	34	21 (62)		34	20 (59)	
≥ 6	51	21 (41)		47	14 (30)	
Pumping frequency on day 4, No. times			.11			.16
< 6	20	13 (65)		18	10 (56)	
≥ 6	65	29 (45)		62	23 (37)	

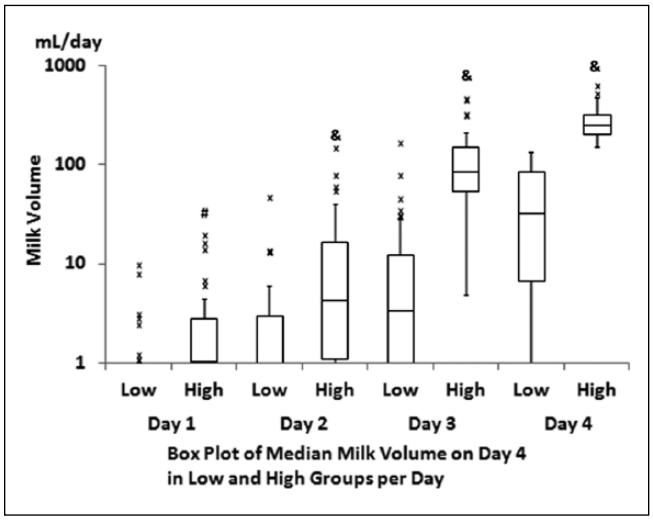
(continued)

Table 1. (continued)

Characteristic[a]	No. per Stratum[b] (Day 4)	Day 4 Milk Volume < 153 mL (Median)		No. per Stratum[c] (Discharge)	Formula Feeding at Discharge	
		No. (%)	*P* Value		No. (%)	*P* Value
Milk volume on day 1, mL			.01			.04
0	43	27 (63)		39	21 (54)	
> 0	42	15 (36)		42	13 (31)	
Milk volume on day 2, mL			< .01			.29
< 2	44	29 (66)		42	20 (48)	
≥ 2	41	13 (32)		39	14 (36)	
Milk volume on day 3, mL			< .01			< .01
< 28	43	35 (81)		41	23 (56)	
≥ 28	42	7 (17)		40	11 (28)	
Milk volume on day 4, mL			< .01			< .01
< 153	42	42 (100)		38	24 (63)	
≥ 153	43	43 (0)		41	8 (20)	

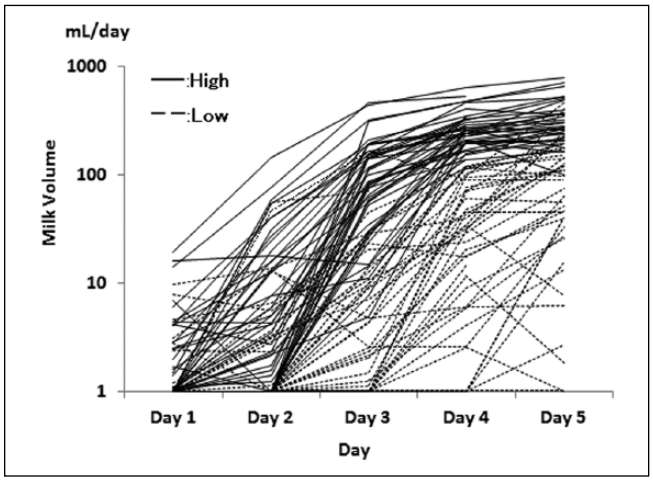
[a]Strata cut-offs for quantitative measures represent greater than or equal to versus less than median except milk volume on day 1. Since median milk volume on day 1 is 0 mL, milk volume on day 1 is categorized as median or greater than median.
[b]Results are based on those with available data at day 4.
[c]Six were excluded from the analysis for this outcome.
[d]Z-score was derived from Japanese standard for birth weight by gestational age.[10]
[e]Two transferred to another hospital before 36 weeks corrected age.

Figure 1. Median Milk Volume, Days 1 to 4 Postpartum, Stratified by Day 4 Milk Volume Group.



The cohort is grouped based on day 4 milk volume: high = milk volume on day 4 greater than or equal to median (≥ 153 mL); low = milk volume on day 4 less than median (< 153 mL). Daily milk volumes are shown as median (bar), quartile range (box), 1.5 quartile range (whisker), and individual outliers (x). For the purpose of plotting the results on a log 10 scale, milk volumes between 0 and 1 were treated as 1 mL. Median milk volume in the low group is 0 mL on days 1 and 2. Median milk volume in the high group is 1 mL on day 1. In some cases, upper quartile, median, and lower quartile were 0 to 1 mL and thus do not appear in the figure. #$P < .05$. &$P < .01$.

Figure 2. Individual Milk Volume Trend over the First 5 Days Postpartum.



Milk volume trajectories are shown for each individual mother, days 1 to 5 postpartum. The cohort is grouped based on day 4 milk volume: high (solid lines) = milk volume on day 4 greater than or equal to median (≥ 153 mL); low (dashed lines) = milk volume on day 4 less than median (< 153 mL). N = 85, days 1 to 4; and N = 74, day 5. The largest milk volume on day 5 is 780 mL.

significant predictors, and lower pumping frequency was no longer a significant predictor, of low milk volume on day 4 (Table 2, model 4).

Distribution of the Study Characteristics by Delivery Mode

Since mothers with a cesarean delivery may differ in other ways from mothers who delivered vaginally, we examined study characteristics stratified by delivery mode (Table 3). Mothers who delivered by cesarean had significantly higher

Table 2. Logistic Regression Models Predicting the Odds of Day 4 Milk Volume < 153 mL.

Model	Reference Stratum[a]	Odds Ratio	95% Confidence Interval	*P* Value
Model 1 (AIC 117)				
Maternal age ≥ 33 y	< 33	2.52	1.05-6.09	.04
Model 2 (AIC 114)				
Cesarean delivery	Vaginal	4.32	1.50-12.41	< .01
Model 3 (AIC 118)				
Pumping frequency < 4 on day 2	≥ 4	3.00	1.18-7.61	.02
Model 4 (AIC 103)				
Maternal age ≥ 33 y	< 33	2.78	1.07-7.11	.03
Cesarean delivery	Vaginal	3.44	1.07-11.03	.04
Pumping frequency < 4 on day 2	≥ 4	2.04	0.71-5.81	.18
Model 5 (AIC 111)				
Maternal age ≥ 33 y	< 33	2.74	1.08-6.96	.07
Cesarean delivery	Vaginal	4.63	1.56-13.76	< .01

Abbreviation: AIC, Akaike's information criterion.
[a]Strata cut-offs for quantitative measures represent greater than or equal to versus less than median.

Table 3. Distribution of the Study Characteristics by Delivery Mode.

Characteristic[a]	No. per Stratum[b]	Cesarean Delivery, No. (%)	*P* Value
Maternal			
Age, y			.92
< 33	39	28 (72)	
≥ 33	48	34 (71)	
Body mass index, kg/m^2			.26
< 20	44	29 (66)	
≥ 20	43	33 (77)	
Pregnancy-induced hypertension			.04
Yes	15	14 (93)	
No	72	48 (67)	
Parity			.18
Primiparous	53	35 (66)	
Multiparous	34	27 (79)	
Infant			
Gestational age, wk			.86
< 29	37	26 (70)	
≥ 29	50	36 (72)	
Birth weight, g			.11
< 1125	43	34 (79)	
≥ 1125	44	28 (64)	
Z-score at birth[c]			.02
< –0.67	42	35 (83)	
≥ –0.67	45	27 (60)	
Day of life at discharge[d]			.76
< 92	42	29 (69)	
≥ 92	43	31 (72)	
Corrected age at discharge, wk[d]			.03
< 42	36	21 (58)	
≥ 42	49	39 (80)	

(continued)

Table 3. (continued)

Characteristic[a]	No. per Stratum[b]	Cesarean Delivery, No. (%)	*P* Value
Milk expression			
Initiation time, h			< .01
< 20	43	23 (53)	
≥ 20	44	39 (89)	
Pumping frequency on day 1, No. times			< .01
0	29	28 (97)	
≥ 1	58	34 (59)	
Pumping frequency on day 2, No. times			< .01
< 4	30	29 (97)	
≥ 4	57	33 (58)	
Pumping frequency on day 3, No. times			< .01
< 6	36	34 (94)	
≥ 6	51	28 (55)	
Pumping frequency on day 4, No. times[e]			.03
< 6	21	19 (90)	
≥ 6	65	43 (66)	
Milk volume on day 1, mL			.01
0	43	36 (84)	
> 0	44	26 (59)	
Milk volume on day 2, mL			< .01
< 2	44	37 (84)	
≥ 2	43	25 (58)	
Milk volume on day 3, mL			< .01
< 28	43	25 (58)	
≥ 28	44	37 (84)	
Milk volume on day 4, mL[f]			< .01
< 153	42	36 (86)	
≥ 153	43	25 (58)	

[a]Strata cut-offs for quantitative measures represent greater than or equal to versus less than median except milk volume on day 1. Since median milk volume on day 1 is 0 mL, milk volume on day 1 is categorized as median or greater than median.
[b]Results are based on cohort with available data at day 4.
[c]Z-score was derived from Japanese standard for birth weight by gestational age.[10]
[d]There are 2 missing data for this variable.
[e]There is 1 missing datum for this variable.
[f]There are 2 missing data for this variable.

prevalence of PIH, later milk expression initiation time, lower pumping frequency from days 1 to 4, and lower milk volume from days 1 to 4. Further, their infants were more likely to have a lower weight-for-age z-score at birth and to be discharged at a later corrected gestational age. Thus, many factors thought to be associated with suboptimal milk production were highly prevalent in mothers who delivered by cesarean.

Predictors of Formula Feeding at the Time of NICU Discharge

Forty-two percent of premature infants were being fed infant formula upon discharge. The unadjusted bivariate associations with this outcome are shown in Table 1.

None of the maternal or premature infant characteristics listed in Table 1 were associated with formula feeding at discharge. Milk expression variables at least marginally associated ($P < .10$) with formula feeding at discharge were later milk expression initiation time, lower pumping frequency on days 1 and 3, and lower milk volume on days 1, 3, and 4.

Logistic regression analyses of the independent predictors of formula feeding at discharge are shown in Table 4. Among the variables in their respective series, pumping frequency on day 3 and milk volume on day 4 showed the strongest bivariate associations with formula feeding at discharge and thus were selected for multiple variable analyses. In a model that included the latter 2 variables and timing of milk expression initiation, pumping frequency on day 3 and later milk expression initiation time were no longer significantly associated with formula feeding at discharge (Table 4, model 4). In this model, lower milk volume on day 4 was associated with 6.3-fold greater odds of formula feeding at discharge.

Table 4. Logistic Regression Models Predicting the Odds of Formula Feeding at Discharge.

Model	Reference Stratum[a]	Odds Ratio	95% Confidence Interval	*P* Value
Model 1 (AIC 106)				
Initiation time ≥ 20 h postpartum	< 20	2.48	1.00-6.15	.05
Model 2 (AIC 107)				
Pumping frequency < 6 on day 3	≥ 6	3.37	1.33-8.50	.01
Model 3 (AIC 94)				
Milk volume < 153 mL on day 4	≥ 153	7.07	2.56-19.52	< .01
Model 4 (AIC 93)				
Initiation time ≥ 20 h postpartum	< 20	2.39	0.81-7.07	.11
Milk volume < 153 mL on day 4	≥ 153	6.27	2.18-18.03	< .01
Pumping frequency < 6 on day 3	≥ 6	1.85	0.63-5.42	.26

Abbreviation: AIC, Akaike's information criterion.
[a]Strata cut-offs for quantitative measures represent greater than or equal to versus less than median.

Discussion

Primary Findings

There are at least 3 notable findings resulting from this retrospective analysis of 87 Japanese mothers who delivered prematurely. First, the strongest predictors of low milk volume on day 4 were cesarean delivery and older maternal age. Second, in unadjusted models, delayed milk expression initiation was marginally associated with day 4 milk volume and significantly associated with formula feeding at discharge. Third, low milk volume on day 4 was a significant predictor of formula feeding at discharge, even after adjusting for milk expression initiation time and pumping frequency on day 3.

Low Milk Volume on Day 4

Our results revealed cesarean delivery to be a strong risk factor for low milk volume on day 4 postpartum. This finding is consistent with others who have reported cesarean delivery to be a risk factor for delayed onset of lactogenesis[11,12]; however, some have not found cesarean delivery to be a risk factor for low milk volume on day 4 postpartum.[13] Less clear are the underlying causal actions that are suppressing the onset of copious milk production in mothers with a cesarean delivery, particularly considering that cesarean delivery represents a more complicated postpartum picture than a mother who delivers a premature infant vaginally. For example, 94% of mothers in our cohort with PIH delivered by cesarean; therefore, in a post hoc subgroup analysis, we compared the odds of low milk volume on day 4 separately for cesarean delivery mothers with and without PIH (vs vaginal delivery). After adjusting for maternal age and pumping frequency on day 2, the PIH group had higher odds of low milk volume on day 4 than the non-PIH group (data not shown). Thus, poor maternal health may underlie at least part of the observed relation between cesarean delivery and low milk volume.

Mothers who delivered by cesarean also expressed their breast milk less often over the first 4 days postpartum. Chen et al[14] reported that breastfeeding frequency on day 2 was positively correlated with milk volume on day 5 postpartum. We found low pumping frequency to be associated with low milk volume on day 4 in an unadjusted model but not in a model adjusted for cesarean delivery. Given the strong covariance between cesarean delivery, PIH, and suboptimal early breast expression patterns (delayed milk expression initiation time and low pumping frequency over the first 4 days), cesarean delivery may represent a composite of many underlying factors that combine to increase the risk of low milk volume on day 4 postpartum.

Older maternal age was also associated with low milk volume on day 4, and this is consistent with previous reports of higher prevalence of delayed onset of lactogenesis in older first-time mothers.[15]

Milk Expression Initiation Time

The median timing of milk expression initiation in this cohort was 20 hours postpartum, which is later than the recommended timing of within 6 hours following delivery.[16] Seventeen percent of mothers initiated milk expression within 6 hours following delivery. Milk expression initiation < 6 hours was not associated with low milk volume on day 4. However, the small number of women who initiated milk expression within 6 hours limits our statistical power to conduct a meaningful analysis.

Milk expression initiation time < 6 hours was also not associated with formula feeding at discharge. Among 6 previous reports, milk expression initiation time was significantly associated with sustained provision of MOM in 2 studies,[17,18] trended toward an association in 1 study[19] and was not associated in 3 studies.[20-22] Factors such as how expression initiation is defined, range and degree of variation in initiation times within each cohort, model covariates, and

the specific outcome examined likely contribute to variation in results. Thus, the importance of milk expression initiation time for sustained provision of MOM requires further study.

Formula Feeding at Discharge

Fifty-eight percent of mothers were exclusively feeding MOM at discharge. To our knowledge, this is the first analysis based on a Japanese cohort to report the breast milk feeding rate at the time of premature infants' discharge from the NICU. Although not an entirely congruent comparison, our rate of exclusively feeding MOM at discharge is considerably higher than the rate reported by Mamemoto et al[23] for Japanese mothers who delivered low birth weight infants (23%) but is similar to that reported by Zachariassen et al[24] for mothers who delivered at < 32 weeks' gestational age (60%).

We found the strongest predictor of formula feeding at discharge to be low breast milk output on day 4. Among mothers producing < 153 mL on day 4 postpartum, 63% of their infants were receiving formula at the time of NICU discharge. In contrast, among premature infants of mothers who produced ≥ 153 mL, only 20% were receiving formula at discharge. Similarly, Hill and Aldag[25] found that mothers who expressed < 140 mL on day 4 had an 8-fold greater risk of inadequate milk volume at 6 weeks postpartum as compared to mothers who expressed > 140 mL on day 4. These findings are consistent with reports that delayed onset of lactogenesis in mothers who deliver at term is associated with shortened breastfeeding duration.[26-28] Thus, an accumulation of evidence suggests that failure to initiate copious milk output within the first 4 days postpartum may increase the risk of future difficulty in achieving or sustaining exclusive breastfeeding.

Limitations, Conclusions, and Next Steps for Future Research

This retrospective study is based on a small to moderately sized data set from a single university hospital cohort, which may limit generalizability to other Japanese NICU settings and beyond. Our study population was similar in the incidence of pregnancy-induced hypertension, diabetes mellitus, and cesarean delivery, and our median maternal age was just slightly older (33 vs 31 years), as compared to the rates reported for the Neonatal Research Network of Japan.[7] Thus, our results appear generalizable with respect to maternal characteristics within Japanese NICU settings.

Another consideration in assessing the generalizability of our results is variation in breast milk expression practices across Japanese NICUs. The Japanese National Survey of Breastfeeding reported that 71% of Japanese NICUs assist mothers in initiating hand expression of breast milk.[6] The same survey reported that 47% of institutions provide mothers with their first instructions on how to express their breast milk during the day shift, on either the day of birth or the day after. Although hand expression of colostrum is gaining favor in the United States,[29] a recent Japanese randomized controlled trial of mothers who delivered at < 32 weeks' gestation found significantly greater milk volumes, less fatigue, and less pain in the group who used an electric pump versus hand expression of colostrum.[30] Thus, further study of the optimal mode of initiating breast expression is urgently needed. At Showa University Hospital, as is common among Japanese hospitals, the practice of delaying initiation of milk expression until the start of the day shift is an obvious barrier to early initiation of milk expression. Greater awareness of the detrimental effects of delayed initiation of breast expression is needed among Japanese NICU health care providers.[19] Nonetheless, Showa University appears quite typical of Japanese NICU breast milk expression practices.

As is true for most retrospective chart reviews, we were not able to examine some variables that have been reported to influence breastfeeding success such as socioeconomic status,[18,25,31-33] previous breastfeeding status,[34] maternal obesity,[15] smoking,[24] antenatal steroids,[35] skin-to-skin contact,[36] and breastfeeding intentions.[18,37-39] We do not have data on smoking or use of antenatal steroids. The smoking rate in our setting was low (9%).[8] Steroids are very routine; approximately 90% of women who deliver premature receive steroids. With regard to skin-to-skin contact, mother and infant dyads practice skin-to-skin contact as soon as the infant's status is stabilized, even if the infant needs mechanical ventilation. Since we do not record skin-to-skin contact frequency in the medical record, we could not analyze the association between skin-to-skin contact and early and sustained milk production. Regarding breastfeeding intentions, it is likely that the majority of the mothers in our study intended to breastfeed, based on the 95% intention rate reported in Japanese national surveys.[40]

Overall, this report adds significant knowledge to the literature, as it is 1 of the most comprehensive analyses to date to examine the provision of MOM with a focus on a setting that is typical among mothers who deliver at less than 32 weeks' gestation in Japan. Our results point to milk volume on day 4 and breast expression initiation time as key factors for sustained provision of MOM. Since the median breast expression initiation time in our study group was delayed until nearly day 2 postpartum (20 hours), and everyone initiated breast milk expression by hand, we were not able to determine the effects of very early initiation or the effects of hand versus mechanical expression on day 4 milk volume.

Conclusion

Further research is needed to identify additional determinants of day 4 milk volume, including the role of maternal health and early interventions, such as the timing and mode of initiating breast milk expression. Accordingly, advances in improving day 4 milk output offer promise toward

increasing the provision of MOM as the sole source of milk for the premature infant throughout the NICU stay and beyond.

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Declaration of Conflicting Interests

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