Delayed lactogenesis in women with insulin-dependent diabetes mellitus[1-4]

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ABSTRACT Breast milk lactose, total nitrogen, conductivity, osmolality, and intake by infants of 33 women with insulin-dependent diabetes mellitus (IDDM), 33 control women without diabetes, and 11 reference women were determined in a 3-mo study of lactation. Milk of women with IDDM had significantly lower lactose and higher total nitrogen (2–3 d postpartum), and their infants had significantly less milk intake (7–14 d postpartum) than did control or reference women. Total nitrogen was negatively correlated with milk lactose for women with IDDM at all times and for control women through day 14 postpartum. The data indicate delayed lactogenesis for women with IDDM, which was more likely to occur with poor metabolic control. Differences in milk composition of women with IDDM do not preclude them from breast-feeding their infants. *Am J Clin Nutr* 1993;58:54–60.

KEY WORDS Lactation, initiation of lactation, breast-feeding, human milk, milk composition, insulin-dependent diabetes mellitus, metabolic control, breast milk intake, test weighing

Introduction

The ability of some women with insulin-dependent diabetes mellitus (IDDM) to breast-feed has been documented (1, 2) as has preliminary information on the unique aspects of their clinical management (2). Although women with IDDM choose to breast-feed as often as do women without diabetes (2), clinical research concerning lactation in women with IDDM is limited.

Milk lactose is thought to be a marker for lactogenesis (3, 4). Lactose increases while protein, sodium, and chloride decrease (5, 6); these changes precede the increase in milk volume secretion (7). Arthur et al (4) found that the onset of copious milk secretion at 24–48 h postpartum, was delayed significantly in women with IDDM; however, breast milk lactose reached a plateau by day 4 postpartum in women with and without IDDM. Bitman et al (8) studied one woman with IDDM and determined that milk volume at 3 d postpartum was lower than that of a normal reference group but normalized by day 5 postpartum.

Euglycemia may influence milk composition and ultimately affect lactation outcome. Hyperglycemia in alloxan-induced diabetic rats or goats resulted in decreased milk lactose and protein (9, 10). Milk yields were also decreased. Insulin administration reversed these effects; however, permanent loss of mammary gland function occurred when insulin was withheld (11). At 90 d postpartum, Butte et al (12) studied breast milk of women with IDDM who had elevated hemoglobin (Hb) A_{1c} concentrations. Breast milk lactose and protein were the same as that of a reference population but glucose and sodium were significantly higher. Hypoglycemia may also occur in women with IDDM; it has been found in the early postpartum period and after breast-feeding (2, 13). Hypoglycemia in animals increased epinephrine, which in turn decreased blood flow to the mammary gland (14, 15). Decreased lactate with increased ketone production was accompanied by decreased mammary gland lipogenesis (16). Ultimately breast milk composition may be affected.

Because breast milk composition of women with IDDM and intake by their infants have not been evaluated longitudinally, the present study investigated lactation in women with IDDM by determining for 3 mo breast milk composition of lactose, total nitrogen, conductivity, osmolality, and intake by infants of women with IDDM. Electrical conductivity was used to measure anion and cation changes in milk that occur with the initiation of lactation (17). If milk of women with IDDM differs in lactose and electrolytes, then milk osmolality might also be affected. Morriss (18) has reviewed the effects of hyperosmolar milk on infant conditions. Because women with IDDM must depend on exogenous insulin to maintain euglycemia and fine-tuned control is difficult to achieve, we also wished to study the effect of metabolic control in women with IDDM on the above markers of lactogenesis and intake by their infants.

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Methods

Subjects

The study population consisted of 33 lactating women with IDDM, 33 lactating women without IDDM (control subjects), and 11 healthy reference women as outlined previously (19). The study had human subjects approval by all hospitals used for recruiting (19) and by the University of Connecticut. Women were recruited through private obstetricians' offices and high-risk prenatal screening clinics at three medical centers. Data on breast milk intake were obtained from a subgroup of mothers who did not differ from the study population with respect to subject characteristics. This subgroup was determined solely by the willingness of the mother to participate. This subgroup included 18 lactating women (control) pair-matched to 18 women with IDDM, 10 reference women, and their infants. Matching characteristics of the subgroup were as follows: gestational age, < 37 ($n = 1$) and ≥ 37 wk ($n = 17$); delivery method, vaginal ($n = 7$) and cesarean section ($n = 11$); infant sex, males ($n = 12$) and females ($n = 6$); prior lactation, yes ($n = 9$) and no ($n = 9$). Five of the 10 reference women had prior lactation experience, and the sex of their infants was 5 males and 5 females.

Collection procedures

Subjects were visited at days 2 and 3 postpartum in the hospital and at days 7 ± 1, 14 ± 2, and 42 and 84 ± 4 postpartum in the hospital or at home (19). Blood samples were drawn 80 min after breakfast. HbA_{1C} samples, drawn at 3 and 42 d postpartum, were transported immediately on wet ice packs to the hospital laboratory or sent by overnight mail in styrofoam containers. HbA_{1C} samples were sent to Smith Kline Bio-Science Laboratories (63.0%) (Waltham, MA) or Nichols Institute (37.0%) (San Juan Capistrano, CA) for analysis. An HPLC analyzer and Hb autodiluter semiautomated system were used. There were no significant differences in average HbA_{1C} concentrations with respect to the laboratory where analyzed; therefore, the data were combined for subsequent analyses. Capillary blood samples were analyzed for glucose at each visit. Either an Accu-Chek bG (Boehringer-Mannheim, Indianapolis) or a Glucoscan 2000 (Lifescan, Mountain View, CA) reflectance meter was used. Both instruments were reported to accurately reflect venous glucose (20).

All milk samples were collected by trained researchers using an Egnell electric pump (Egnell Inc, Cary, IL). Milk expression was done immediately after blood glucose was determined. To ensure a representative milk sample, mothers were asked to breast-feed their infants before breakfast, thus ensuring a 1-h interval between breast-feeding and sampling. The breast pump was held to the breast until milk no longer came out in an even intermittent stream, ≈ 8 min/breast. At days 2 and 3 postpartum the mothers' breasts were pumped for a maximum of 5 min if no sample was available. The procedure always began on the right breast and was repeated for the left breast. All analyses were done on samples from both left and right breasts. Samples for nutritional analyses were immediately frozen at the collection site on dry ice and transferred to a freezer (-70 °C) until analyzed. When there was adequate milk, fresh milk for conductivity and osmolality was sampled, transported to the laboratory on a wet ice pack, and analyzed within 4 h.

Breast milk intakes were determined at 7, 14, 42, and 84 d postpartum by test weighing the infant before and after each feeding for 24 h plus one more feeding. A model 3862MP8 (Sartorius, Gottingen, Germany) integrating electronic balance equipped with a printer and infant seat was used. The balance integrates repetitive weighings every 2 s; precision stated by the manufacturer is ± 0.05 g. The balance was placed on a level surface and calibrated in the home by the researcher. Verbal and written instructions were given and mothers demonstrated their ability to use the balance. Mothers were asked to follow their usual daily feeding routine noting any feedings in which formula was used. For 7 of the 17 formula feedings, test weighing was not possible and intake was measured as volume removed from the bottle.

The 24-h milk intake was calculated by *1*) summing the difference of the before and after weights for each feeding, *2*) subtracting the gram intake of the last feeding from the day's total (24 h plus 1 feeding) because intake from the next-to-last feed satiated the infant until the time of the last feed, and *3*) extrapolating to an exact 24-h period. The data used represented time spans of 24 ± 3 h.

Metabolic control of women with IDDM

Postpartum metabolic control was determined by using White's classification (19, 21), HbA_{1C} at 3 and 42 d postpartum, and fasting blood glucose (FBG) and blood glucose at 80 min after breakfast at each visit. Appropriate FBG concentrations are 3.9–6.7 mmol/L (22). Blood glucose variability can be measured through continuous monitoring of blood glucose patterns and calculation of the mean amplitude of glycemic excursions (MAGE) (23). Blood glucose at 80 min after breakfast correlates best with MAGE (24). Determination of MAGE was not possible in our study; therefore, the 80-min postprandial glucose (PPG) value was used. PPG should be $<$ 8.9–10.0 mmol/L at 90 min (22). We considered an appropriate concentration for PPG at 80 min to be 8.9 mmol/L.

Milk sample analysis

Glucose and lactose were determined by using the model 27 industrial analyzer (Yellow Springs Instrument Co, Inc, Yellow Springs, OH) (25). Total nitrogen was determined by the micro-Kjeldahl method (26) by using the Tecator 1009 Digestion System and Tecator-Kjeltec System 1002 Distilling Unit (Höganäs, Sweden). Conductivity was determined by using a model 35 Conductance Meter (Yellow Springs Instrument Co, Inc) calibrated with potassium chloride (27). Osmolality was determined by freezing-point measurement with a model 5004 μOsmette (Precision Systems, Inc, Natick, MA) calibrated with sodium chloride (28). All milk samples were analyzed in duplicate.

Statistical analysis

All statistical tests were done by using *SAS* (29, 30). When P equalled 0.01 it is stated, otherwise $P < 0.05$ is assumed. Paired t tests were used to determine differences between the left and right breasts. Because breast milk composition did not differ significantly between breasts, the average was calculated. A repeated-measures (split-plot) analysis of variance (ANOVA), using the main effects of group, individual within group, time, and group-by-time interaction, was used to determine group and time differences for milk composition and intake by infants. The protected least-significant difference test was used to make contrasts between each pair of group means (31). The assumption of compound symmetry was checked by using the *REPEATED*

statement. If the compound symmetry assumption was violated ($P < 0.05$), the Huynh-Feldt conservative test was used to check for interaction between group and time. For the covariates 80-min PPG and time from last breast-feeding, a repeated-measures analysis of covariance was accomplished by using *SAS PROC GLM*.

The approximate F statistic was used to test the significance of group-by-time interactions for breast milk intake. The approximate F statistic is calculated from a weighted average of the between- and within-subject mean square error terms in the ANOVA (31). For one-sided tests a power of 80, an effect size of 1.2, and a significance level of 0.05 were used (32). Pilot-study data were used in the power calculations. Minimum sample sizes for a power of 80 were exceeded. Spearman rank correlation coefficients were used for correlations with White's classification. Pearson correlation coefficients were used for milk composition and intake data.

Results

The groups did not differ concerning the time elapsed from breakfast to the sampling of blood and milk. The women with IDDM had a significantly longer time interval between the mother's last breast-feeding and when the milk sample was taken compared with the control and reference women [least-squares means (LSM) ± SEM: 3.76 ± 0.2, 2.56 ± 0.3, and 1.99 ± 0.3 h, respectively; $F = 6.15$; df = 2, 73; $P < 0.01$]. All groups had milk samples taken a minimum of 2 h after the last breast-feeding. When the time interval from the last breast-feeding was used as a covariate, it did not affect the milk-composition results.

The milk of women with IDDM had significantly less lactose (LSM ± SEM collapsed over time: 161.80 ± 3.66 mmol/L) than the milk of control (174.87 ± 2.97 mmol/L) or reference (181.12 ± 3.92 mmol/L) women ($F = 7.00$; df = 2, 70; $P < 0.01$) (**Table 1**). Milk lactose increased significantly over time to 42 d postpartum ($F = 76.22$; df = 2, 70; $P < 0.001$). Breast milk lactose was negatively and significantly correlated with breast milk conductivity at 3 d postpartum for control and reference women ($r = -0.99$). By day 7 postpartum all groups had negative and significant correlations.

Women with IDDM had significantly higher milk total nitrogen at days 2 and 3 postpartum than did control or reference women ($F = 3.18$; df = 2, 68; $P < 0.01$). Total nitrogen was negatively correlated ($P \leq 0.05$) with milk lactose for women with IDDM at days 3–84 postpartum, for control women through day 14 postpartum, and for reference women only at day 2 post-

TABLE 1
Breast milk composition*

Component and group	Days postpartum					
	2	3	7	14	42	84
Lactose (mmol/L)						
IDDM†	95.87 ± 7.13 [6]	159.87 ± 4.18 [17]	163.34 ± 3.02 [29]	178.01 ± 3.44 [24]	185.58 ± 3.83 [20]	188.16 ± 4.05 [18]
Control	130.81 ± 4.58 [14]	163.01 ± 3.36 [24]	175.84 ± 2.97 [29]	185.40 ± 3.38 [24]	192.49 ± 3.56 [22]	201.65 ± 4.23 [16]
Reference	142.80 ± 6.70 [6]	166.38 ± 4.74 [11]	182.08 ± 4.74 [11]	187.89 ± 4.74 [11]	202.00 ± 4.74 [11]	205.60 ± 4.74 [11]
Total nitrogen (g/L)						
IDDM	7.78 ± 0.47 [3]‡	4.78 ± 0.23 [13]‡	3.09 ± 0.15 [25]	2.59 ± 0.16 [24]	2.24 ± 0.18 [20]	2.06 ± 0.19 [18]
Control	5.46 ± 0.29 [8]	3.49 ± 0.17 [22]	3.02 ± 0.15 [26]	2.49 ± 0.16 [24]	2.16 ± 0.17 [21]	1.89 ± 0.21 [14]
Reference	5.41 ± 0.31 [6]	3.38 ± 0.25 [9]	2.94 ± 0.22 [11]	2.49 ± 0.22 [11]	2.10 ± 0.22 [11]	1.82 ± 0.22 [11]
Conductivity (Ω)§						
IDDM		0.28 ± 0.02 [5]	0.31 ± 0.01 [17]	0.29 ± 0.01 [15]	0.25 ± 0.01 [14]	0.25 ± 0.02 [11]
Control		0.32 ± 0.02 [7]	0.29 ± 0.01 [20]	0.25 ± 0.01 [19]	0.20 ± 0.01 [19]	0.21 ± 0.01 [16]
Reference		0.34 ± 0.02 [8]	0.27 ± 0.01 [11]	0.25 ± 0.01 [11]	0.21 ± 0.01 [10]	0.20 ± 0.01 [11]
Osmolality (mOsmol/kg)§						
IDDM		276.24 ± 9.09 [5]	297.98 ± 4.34 [16]	292.09 ± 4.55 [15]	279.02 ± 4.86 [14]	286.89 ± 5.54 [11]
Control		287.16 ± 7.04 [7]	290.19 ± 3.92 [20]	286.64 ± 4.22 [18]	290.75 ± 3.96 [20]	298.09 ± 4.52 [16]
Reference		293.15 ± 6.01 [8]	295.77 ± 4.95 [11]	296.95 ± 4.95 [11]	292.79 ± 5.27 [10]	290.45 ± 4.95 [11]
Milk intake of infants (g/d)‖						
IDDM¶			309.62 ± 32.37 [15]	426.05 ± 32.28 [15]	575.29 ± 33.98 [14]	530.93 ± 39.47 [11]
Control¶			455.46 ± 29.71 [17]	504.80 ± 35.69 [13]	535.35 ± 36.04 [13]	511.95 ± 39.81 [11]
Reference			518.50 ± 38.20 [10]	592.17 ± 40.93 [9]	654.43 ± 38.20 [10]	673.72 ± 38.20 [10]
Milk and formula intake of infants (g/d)‖						
IDDM			329.89 ± 27.63 [15]‡	447.10 ± 27.55 [15]**	624.70 ± 29.01 [14]	580.72 ± 33.69 [11]
Control			456.52 ± 25.36 [17]	516.49 ± 30.46 [13]	542.44 ± 30.76 [13]	588.59 ± 33.98 [11]
Reference			528.12 ± 32.60 [10]	595.36 ± 34.93 [9]	654.43 ± 32.60 [10]	684.33 ± 32.60 [10]

* Least squares means ± SEM. When group names are footnoted, group least-squares means collapsed over time are statistically different. n in brackets.
†‡ Significantly different from both control and reference: †$P < 0.01$, ‡$P < 0.05$.
§ Data not available at 2 d postpartum.
‖ Data not available at 2 or 3 d postpartum.
¶** Significantly different from reference: ¶$P < 0.01$, **$P < 0.05$.

partum. Correlations ranged from −0.57 to −0.76 for women with IDDM and from −0.43 to −0.80 for control women; the value for reference women was −0.87 at day 2 postpartum. We graphed lactose and total nitrogen together to study their relationship as an index of lactogenesis. Although lactose and total nitrogen intersect at similar concentrations for all groups, the intersection occurs earliest in reference women, followed by control, then women with IDDM (**Fig 1**).

Breast-milk conductivity and osmolality did not differ among the three groups. Milk conductivity decreased significantly over time from 7 to 42 d postpartum (F = 21.12; df = 2, 54; P < 0.001). Milk lactose (r = 0.36, 0.29), total nitrogen (r = −0.26, −0.14) and conductivity (r = −0.37, −0.19) were significantly correlated with feeding frequency for women with IDDM and control women, respectively. Milk intake was significantly correlated with feeding frequency for women with IDDM at 14 (r = 0.57) and 42 d postpartum (r = 0.81), for control women at 84 d postpartum (r = 0.72), and for reference women at 42 d postpartum (r = −0.78).

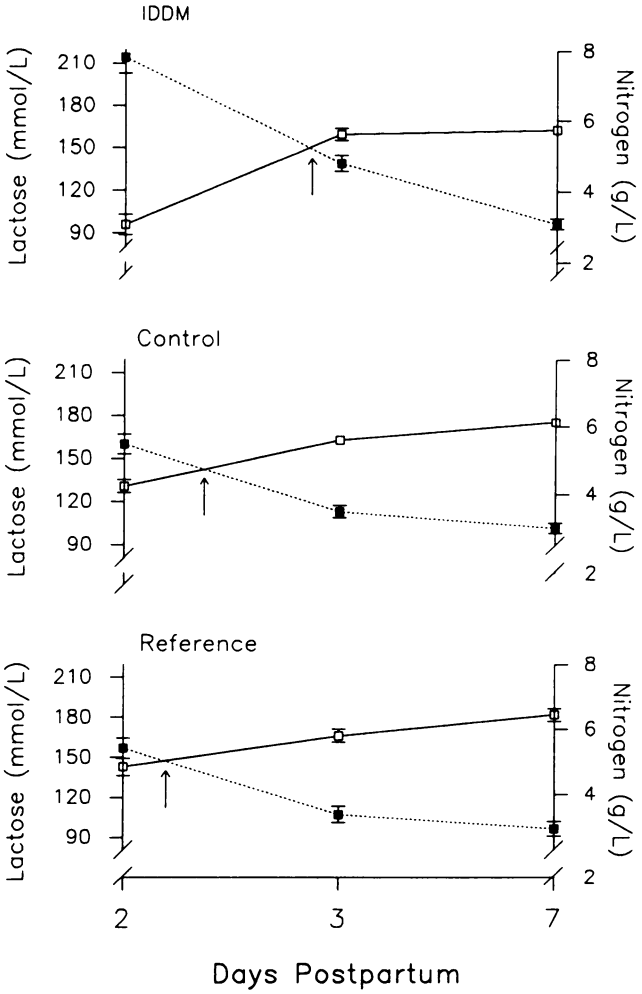

FIG 1. Breast milk lactose (□) and total nitrogen (■), concentrations for women with insulin-dependent diabetes mellitus (IDDM) and control and reference women. Least squares means ± SEM, except when the SEM is smaller than the diameter of the symbol. *See* Table 1 for number of subjects. The point of intersection is used as an index of lactogenesis. Lactogenesis occurred first in reference women, then in control women, and finally in women with IDDM.

Infants of women with IDDM and control women consumed significantly less breast milk (g/d) than did infants of reference women (F = 4.69; df = 2, 43) (Table 1). Infant milk intake was significantly correlated with breast milk lactose and conductivity (negatively) for women with IDDM at 7 (r = 0.57, −0.81, respectively) and 14 (r = 0.56, −0.76, respectively) d postpartum, and at 7 (r = 0.68, −0.75, respectively) d postpartum for control women. Milk intake of infants of women with IDDM was also significantly negatively correlated with total nitrogen at 7 (r = −0.64) and 14 (r = −0.53) d postpartum. Infants of women with IDDM consumed significantly less breast milk and formula combined than did infants of control women at 7 d postpartum and of reference women at 7 and 14 d postpartum (F = 2.58; df = 2, 43).

The mean HbA_{1C} concentration at 3 and 42 d postpartum was within normal limits for women with IDDM; however, it was significantly higher than in the other groups (LSM ± SEM: IDDM 5.54 ± 0.11%, control 4.16 ± 0.10%, and reference 4.33 ± 0.13%; F = 14.17; df = 2, 71; P < 0.001). The majority (53%) of the women with IDDM had an FBG ≤ 6.7 mmol/L at all times. Women with IDDM had significantly higher 80-min PPG concentrations than did control or reference women (LSM ± SEM: 13.6 ± 0.3, 5.6 ± 0.3, and 5.7 ± 0.4 mmol/L, respectively; F = 82.12; df = 2, 74; P < 0.001). The average PPG concentration for women with IDDM ranged between 11.6 ± 0.7 and 15.6 ± 0.7 mmol/L throughout the study. A minimum of 72% of these women had values > 8.9 mmol/L at each time point.

White's classification was significantly correlated with total milk nitrogen at day 3 postpartum (r = 0.38) and negatively with lactose at days 7 (r = −0.25) and 84 postpartum (r = −0.42). There were no significant correlations between HbA_{1C} and milk composition. FBG correlated significantly with total nitrogen at 2 d postpartum (r = 0.99). Women with IDDM with an FBG > 6.7 mmol/L had greater milk conductivity at 7 d postpartum than did women with IDDM with an FBG ≤ 6.7 mmol/L; they also had greater milk conductivity than control or reference women (F = 3.17; df = 3, 39; P < 0.001).

Women with IDDM with a PPG > 8.9 mmol/L had total milk nitrogen at 2 d postpartum and osmolality at 3 d postpartum significantly higher than values for women with IDDM with a PPG ≤ 8.9 mmol/L and control and reference women. Milk composition of women with a PPG ≤ 8.9 mmol/L did not differ significantly from that of control or reference women. Infants of women with PPG > 8.9 mmol/L had significantly less milk intake than did infants of women with a PPG ≤ 8.9 mmol/L at 7 (F = 5.21; df = 3, 38; P < 0.01) and 14 (F = 3.18; df = 3, 33) d postpartum. Milk lactose of women with an FBG > 6.7 mmol/L or a PPG > 8.9 mmol/L was consistently lower at 2, 7, and 14 d postpartum (NS).

When PPG was used as a covariate, infants of women with IDDM had significantly less milk intake than did the reference infant group at 7, 14, and 84 d postpartum and than did the control infant group at 84 d postpartum (F = 2.27; df = 2134). Without the covariate, group means collapsed over time were significantly different. The adjusted group means for milk intake for women with IDDM increased at 7, 42, and 84 d postpartum but remained essentially unchanged for the other groups.

Discussion

A delay in the initiation of lactation in women with IDDM is indicated by the lower milk lactose and lower breast milk intakes of their infants. Arthur et al (4) also found that mothers with IDDM had a delay of 28 h for milk lactose to reach comparable concentrations found in women without diabetes.

The higher nitrogen content in the milk of women with IDDM at 2-3 d postpartum in the present study also suggests delayed lactation. Kulski and Hartmann (5) found a dramatic decrease in milk total protein consistent with the onset of lactogenesis. To compare our results with theirs, we converted total protein to total nitrogen, using a factor of 6.25 assuming that protein nitrogen comprises 87% of total nitrogen at days 2–3 postpartum (33). In Kulski and Hartmann's (5) study, the derived milk total nitrogen peaked at 11.4 g/L 30 h after delivery and decreased by more than half to 4.1 g/L by 50 h postpartum. If lactogenesis were "on time," the total nitrogen for the women with IDDM (7.8 g/L) should be far less at 45 h from delivery. The total nitrogen of control and reference women followed a similar pattern of decline as that found by Kulski and Hartmann. Breast milk nitrogen of women with IDDM was not similar to that of the other groups until 7 d postpartum.

The negative correlation between lactose and total nitrogen for all groups at 2 d postpartum is consistent with lactogenesis. Others have documented similar negative correlations of lactose and whey proteins (5) or total protein (34) as estimates of the timing of lactogenesis. In the present study the lactose and total nitrogen contents for the reference women were correlated only at day 2 postpartum, indicating subsequent establishment of lactation and corroborating the findings reported previously (5, 34). The negative correlation existed the longest for women with IDDM, indicating a delay in lactogenesis.

Saint et al (3) also found a positive correlation between lactose and milk yield and a negative correlation between total protein and milk yield to be consistent with lactogenesis. The lack of significant correlations between lactose or total nitrogen and breast milk intake for reference women further suggests that lactogenesis likely occurred before the time when breast milk intake was first studied at day 7 postpartum. In contrast, significant correlations still existed for control women at 7 d postpartum and for women with IDDM at 14 d postpartum, which suggests that full lactation could not have been established until after this time.

Before lactogenesis, the paracellular pathway is leaky and sodium, chloride, and water pass into the milk diluting lactose and maintaining osmolality (35). This additional sodium and chloride would increase milk conductivity. However, as lactose increases with established lactation and the paracellular pathway no longer leaks, sodium and chloride, and consequently conductivity, decrease. Delayed lactation for women with IDDM based on milk conductivity is suggested because a negative correlation with lactose was not established until day 7 postpartum and with intake by infants until day 14 postpartum.

The lack of early maternal attachment associated with cesarean section deliveries may be a factor in the delayed lactogenesis for women with IDDM (36). Kulski et al (37) found no difference in milk lactose as a result of cesarean section delivery but suckling began within 12 h after delivery in their study. Women with IDDM first breast-fed their infants at 26.1 ± 2.8 h after delivery (19); therefore, lack of early breast stimulation may have influenced this delay.

It is interesting that feeding frequency was not correlated with milk composition or milk intake for reference women but was for women with IDDM and control women. Similarly, Nommsen et al (38), in their longitudinal study of healthy, exclusively breast-feeding women (< 120 mL/d of other milk or formula), found that breast-feeding frequency was not significant in the regression equations relating to macronutrient milk composition at 3, 6, 9, or 12 mo postpartum when controlled for milk production. Others have also noted no relationship between breast-feeding frequency and milk intake (39–41). It may be that feeding frequency is not an issue for healthy breast-feeding mothers with well-established milk output. However, for women with multiple problems related to their prenatal care and puerperium recovery, such as the women in our study with IDDM and control women, feeding frequency may be an important determinant of breast-feeding success.

A delay in lactogenesis in women with IDDM is postulated on the basis of a comparison with the milk-composition values of the reference women. Milk lactose values for the reference women were similar to those reported at 48–72 h postpartum (3, 7), 42 d postpartum (42), and 3 mo postpartum (38, 43). They were slightly higher than those previously reported for milk from our laboratory: 173 mmol/L at 42 d postpartum and 188 mmol/L at 84 d postpartum (44). Different analytical methods may explain this because in the earlier study an enzymatic method from Boehringer-Mannheim Biochemicals was used (44). Our reference women had slightly lower milk lactose concentrations at 7 and 14 d postpartum than did multiparous women (45) and women in developing nations (46, 47).

The milk total nitrogen concentrations of control and reference women agreed with results of other investigators at 1–3 (33, 48), 7–20 (44, 48, 49), and 90–105 d postpartum (44, 47–49). Lönnerdal et al reported slightly higher total nitrogen in privileged women in Ethiopia (47) and Sweden (50) at 0.5–1.5 mo; however, exact comparison is difficult because different time periods were reported. The breast milk lactose and total nitrogen concentrations of women with IDDM were similar to values reported in the literature (12, 51).

The remarkable stability of milk osmolality found in the present study confirms the findings of some researchers (28, 52, 53), but slightly lower (54) or higher (55) osmolality was found by other investigators. As the secretion of lactose increases to amounts consistent with established lactation, the ionic concentration decreases to maintain milk isoosmotic with plasma (35). The similarity among the groups in milk osmolality and conductivity suggests that even though women with IDDM had significantly lower milk lactose, the ionic concentration was not significantly altered.

Milk-intake data for infants of women with IDDM from other studies is not available. Breast-milk intake of our reference group was ≈50 g/d below that reported by Neville et al (39) for the same infant ages in exclusive breast-feeders. All of their subjects and 50% of our subjects were multiparous. If the multiparous women breast-fed previously, then prior lactation experience could account for the larger intakes (56). Several investigators have reported data at 84–90 d postpartum. Our 84-d value of 674 ± 38 g/d falls at the lower limit of values reported: 676 to 811 ± 133 g/d (38, 43, 57). Differences can be attributed to the large variation in breast milk intake (43), use of a less-accurate

pediatric balance (43), or insensible water loss during breast-feeding (38).

Although infants of women with IDDM received more formula throughout the study than did the infants of control and reference women, group differences in breast milk intake are only offset by the higher formula intake at 42 and 84 d postpartum. One cannot determine whether the infants of women with IDDM who were given formula actually needed a supplement. Perhaps if their mothers had not offered formula, the infants' demand would have stimulated increased breast milk production to a degree that would have satisfied their appetites. Alternatively, without the formula, their nutrition might have been compromised.

The issue of metabolic control during lactation in women with IDDM is not clearly defined. All criteria used to measure metabolic control suggested that good metabolic control is an important determinant of successful lactation, in terms of "normal" milk composition, in women with IDDM. However, no one criterion is a predictor of changes in milk composition.

Women with IDDM with a higher White's classification, and therefore more severe diabetes and/or poorer metabolic control (as measured by HbA_{1C}, FBG, or 80-min PPG), were more likely to have delayed lactogenesis. This is indicated by the negative correlations between White's classification and lactose and the positive correlations between both White's classification and FBG and total nitrogen at 2–3 d postpartum. As initially hypothesized, women with IDDM with good metabolic control had milk composition similar to that of control and reference women, with respect to the nutrients measured in this study. However, women with elevated FBG or 80-min PPG had higher total nitrogen at day 2 postpartum; osmolality at day 3 postpartum; conductivity at day 7 postpartum; lower lactose at days 2, 7, and 14 postpartum; and lower infant milk intake at days 7, 14, and 84 postpartum, which suggests that the delay in lactogenesis was influenced by metabolic control. The increase in the breast-milk intake of infants of mothers with IDDM when the groups were equalized for 80-min PPG further substantiates this conclusion.

Women with IDDM were able to breast-feed and despite significant differences in breast milk lactose and total nitrogen concentrations, milk composition for these nutrients was within accepted ranges. There was a delay in lactogenesis for women with IDDM, indicated by lower milk lactose, higher total nitrogen at 2–3 d postpartum, delayed intersection of lactose and nitrogen when graphed (Table 1), a negative correlation between lactose and nitrogen, a negative correlation between both conductivity and total nitrogen and intake by infants, and lower milk intake by infants of women with IDDM. This delay was correlated with poor metabolic control.

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