

Relationship of breast feeding and weight loss to jaundice in the newborn period: review of the literature and results of a study¹

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A group of 588 consecutively born infants at a community hospital were studied at half-day intervals during their routine hospitalization for jaundice and its relationship to breast milk or formula. Any infant exhibiting a potential risk for jaundice was eliminated from the study. Breast-milk-fed (BMF) infants demonstrated a significantly higher incidence of serum bilirubin (SB) >10 mg/dl and >15 mg/dl ($P < .001$) than formula-fed (FF) infants. In addition, BMF infants exhibited significantly greater weight loss than FF infants. However, when group effect (BMF or FF) on SB levels was adjusted for weight loss by analysis of covariance testing, differences in SB were less significant, suggesting that weight loss may be a contributory factor to the jaundice seen in BMF infants during the first week of life. A review of the literature is included, and a distinction is proposed between prolonged breast milk jaundice and the early exaggeration of physiologic jaundice in BMF infants.

Index terms: Breast feeding • Jaundice

Cleve Clin Q 50:263-268, Fall 1983

The relationship of breast feeding to newborn jaundice, although long ignored, has gained increasing interest as more and more women begin nursing their babies. Physicians often express concern that breast milk fed (BMF) infants seem to exhibit more frequent, pronounced, and prolonged jaundice than do their formula-fed (FF) peers. We review the literature pertinent to this topic and present the results of a study that examined the feeding patterns, serum bilirubin (SB) levels, and daily weights of 588 consecutive live neonates at a community hospital to determine how these variables are interrelated. A distinction in ter-

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minology is proposed between early breast milk jaundice (perhaps an exaggeration of physiologic jaundice associated with the early poor weight gain of BMF infants) and late breast milk jaundice, related to glucuronyl transferase inhibitors in breast milk.

Materials and methods

Laboratory methods

Serum bilirubin levels were determined from blood samples obtained by heel stick, collected into microhematocrit tubes, and analyzed in an American Optical Company Bilirubinometer (#10200). Average standard deviation and coefficient of variation during the duration of the study were 0.3% and 1.89%, respectively.

Patient population

All 588 live infants born at Parma Community General Hospital over a five-month period (October 1982 through February 1983) were initially entered into the study. Eighteen obstetricians and 19 pediatricians were responsible for the delivery and newborn care of all infants. No effort was made to standardize the conditions of labor and delivery or the clinical indications for SB level determinations, phototherapy, or supplemental formula feedings to BMF infants. Epidural analgesia was rare (three instances), and cesarean deliveries were performed when indicated.

An infant was eliminated from the study group if it has been fed breast milk initially but received formula supplementation prior to any SB level determination; however, any BMF infant who had received supplement after an SB level was obtained (or any infant who received phototherapy) was included until supplementation (or phototherapy) was instituted. Other causes for elimination from the study included insufficient laboratory data and any risk factors.

Study design

To avoid additional heel sticks, blood samples for SB levels were obtained at the time of screening for phenylketonuria (PKU), which is required by law in Ohio on all newborns and is routinely performed at the time of discharge from the newborn nursery. In addition, all SB level determinations performed for suspicion of jaundice were also recorded.

The infant's age at the time of each heel stick was rounded to the nearest half day, but since

too few samples were obtained at $\leq$ two days or $\geq$ six days, only data from days 2.5 through 5.5 were analyzed.

In accordance with standard nursery routine, infants were weighed naked at birth and then each morning thereafter, beginning with the second day of life. Infants were offered sterile water at approximately six hours of age, followed by initiation of either demand breast milk or formula feeding, according to the mother's preference. Occasionally, 5% glucose water was offered in addition, if breast feeding was delayed after cesarean delivery.

The following data were also recorded for each infant: birth weight, sex, one and five minute Apgar scores, method of delivery (vaginal/cesarean), reason for cesarean delivery (primary/repeat), mother's blood type and Rh, infant's blood type and Rh (when determined), direct Coombs' test results (performed when indicated), and any perinatal factor that might adversely affect the infant or its SB level.

Statistical methods

The frequencies of occurrence of discrete conditions in infants retained for analysis in the study group, and those eliminated for any reason were compared by chi-square analysis or Fisher's exact test. Differences between BMF and FF infants who were eliminated were similarly compared. Student's t-test was employed to compare group differences in SB levels and percent weight loss at half-day intervals. Analysis of covariance was used to adjust for percent weight loss in the comparison of bilirubin differences.

Results

Of 588 live births, two sick infants were transferred before feeding preference was determined. The remaining 586 infants were entered into the study. To confirm a normal study population, various data collected from the present study were compared with previously published or locally available statistics (*Table I*). The only factor that differed to any extent was the cesarean delivery rate.

In *Table 2*, 123 of the BMF infants and 105 of the FF infants were eliminated for one or more of the factors listed. Thirty-six BMF infants received formula supplement. There were no significant differences between BMF and FF infants regarding their reasons for elimination.

As would be expected, infants who were elim-

Table 1. Characteristics of total infant population

	Present study	Comparative studies*
Mean birth weight (g)	3403	3457 ¹ 3358 ²
Sex ratio (% males)	51.4	51.4 ³ 51.0 [†]
Breast milk fed (%)	52.2	43.4 ⁴ 54.0 ⁵ 55.0 ⁶ 82.0 ⁷
Cesarean delivery (%)	24.1	15.8 [†] 15.2 [†] 16.2 [†]

* Superscripts refer to references.

† Personal communication: Anderson F. Cleveland Metropolitan General Hospital Neonatal Statistical Report, 1979; 1980 and 1981 Annual Report of the Department of Gynecology; 1982 MacDonald House Statistics.

inated differed significantly ($P < 0.01$) from the study population in type of delivery, with a higher incidence of cesarean sections necessitated by fetal distress. There were also significantly more instances of phototherapy ($P = 0.01$), especially among BMF infants who were eliminated. The remaining data refer to the 358 infants in the study population.

Table 3 compares BMF and FF study infants. The two groups do not differ in sex ratio or cesarean delivery rate, but do differ significantly

Table 2. Factors resulting in elimination from study group

	Breast milk fed (Number)	Formula fed (Number)
Total number of infants eliminated	123	105
Reasons for elimination*		
Maternal risk factors [†]	7	7
Fetal distress	8	6
Apgar score < 7 [‡]	4	5
Prematurity [§]	13	12
Birth weight ≥ 4000 g, ≤ 2500 g	41	39
Sickness	7	5
Positive Coombs' test [¶]	4	8
Formula-supplemented breast milk fed infants	36	0
Laboratory data incomplete	41	49

* Groups not mutually exclusive.

† Gestational diabetes, severe pre-eclampsia, placenta previa.

‡ One or five minute Apgar scores.

§ < 38 weeks gestation by date of examination.

|| Respiratory distress syndrome, suspected sepsis, meconium aspiration, or any congenital condition requiring emergency transfer to a level III nursery.

¶ Direct Coombs' test (performed routinely on all infants of Rh negative or type O mothers, or when indicated).

Table 3. Comparison of study group infants

	Breast milk fed	Formula fed
Number of infants (%)	183 (51.1%)	175 (48.9%)
Mean birth weight (g)	3406	3314
Sex ratio (% males)	46.4	52
Cesarean delivery (%)	21.9	17.7
Primary	11.5	4.6
Repeat	10.4	13.1
Number of infants with:		
Peak bilirubin > 10 mg (%)*	73 (39.8)	28 (16)
Peak bilirubin > 15 mg (%)*	8 (4.4)	0 (0)
Phototherapy (%) [†]	7 (3.8)	1 (0.6)

* Chi-square test $P < 0.01$.

† Fisher's exact test $P = 0.08$.

in the reason for cesarean delivery, a relatively higher proportion of FF infants being delivered by repeat section, and correspondingly more BMF infants being delivered by primary section. Although maternal parity was not recorded in this study, Saigal et al¹ noted a disproportionate number of primiparous mothers among their BMF infants. Since all cesarean deliveries in primiparous mothers would be primary, this would tend to increase primary cesarean delivery in this group.

The mean birth weight for FF infants was also slightly higher than for BMF infants ($P = 0.01$), but since previous studies have found no difference in either weight loss or mean SB levels on day 3 in infants with birth weights of 2500–4000 g,⁸ this difference was not considered clinically relevant.

There was a significant difference between BMF and FF infants in the incidence of SB level, > 10 mg/dl and > 15 mg/dl ($P < .01$). Although the two groups do not differ significantly in the use of phototherapy, five additional BMF infants who required phototherapy were eliminated on the basis of formula supplementation before phototherapy.

Table 4 compares mean weight loss (as a percent of birth weight) and mean SB levels between BMF and FF infants. Included are single SB levels determined at discharge, and multiple SB levels on the same infant determined at the attending physician's discretion for suspicion or monitoring of jaundice. For this reason, the absolute values in Table 4 are not indicative of the population as a whole and cannot be compared to other studies in which all infants were tested once at a designated age. However, differences between BMF and FF infants remain valid, since feeding regimen was not a factor in the clinical indications

Table 4. Significance of differences in weight loss and serum bilirubin levels

	Half-day intervals tested						
	2.5	3.0	3.5	4.0	4.5	5.0	5.5
Number of infants studied							
BMF*	34	49	52	58	31	22	13
FF*	19	23	38	41	23	22	9
Mean weight loss (%)							
BMF	5.2	5.3	5.5	5.2	4.5	4.1	4.0
FF	3.6	2.8	3.1	3.1	2.0	2.3	0.8
P value	≤0.01	<0.01	<0.001	<0.01	<0.01	0.12	<0.01
Mean serum bilirubin (mg/dl)							
BMF	10.6	10.7	10.8	8.3	9.9	9.7	8.1
FF	9.5	8.3	7.3	7.6	6.7	6.2	3.8
P value	0.16	<0.01	<0.001	0.35	<0.01	<0.01	0.03
Analysis of covariance†							
P value	0.38	0.01	0.001	0.92	0.14	0.01	0.22

* BMF = breast milk fed, FF = formula fed.

† Group effect (BMF or FF) on serum bilirubin adjusted for weight loss.

for obtaining SB levels. Analysis of the data confirms this objectivity.

The analysis of variance examines the difference in SB levels between BMF and FF infants adjusted for weight loss. Although four of seven half-day intervals show significantly higher SB levels in BMF than FF infants ($P \leq 0.01$), when these differences are adjusted for the significantly higher weight loss sustained in BMF infants ($P < 0.01$ for six or seven half-day intervals), only one interval (3.5 days) remains highly significant ($P = 0.001$), and two other intervals somewhat less so ($P = 0.01$). This suggests that weight loss may be a contributing factor to the higher SB levels observed in BMF infants during the first week of life.

Discussion

The first reports of unexplained prolonged jaundice in BMF infants were published in 1963. Newman and Gross⁹ summarized the case histories of 11 BMF infants referred for evaluation of prolonged jaundice. In some cases, jaundice had become noticeable during the period of initial postpartum hospitalization, but the jaundice always persisted for two to six weeks, unless breast feeding was interrupted, in which case, a more rapid decline in bilirubin occurred.

In the same year, Arias et al¹⁰ also described jaundice (SB level, 15–24.3 mg/dl) in 4 two-week-old breast fed infants, and further studies led to the description of a steroid in maternal milk that inhibited glucuronyl transferase activity.¹¹ Gartner and Arias¹² followed up the clinical course of 20 BMF infants referred for evaluation of jaundice that began after the third (and most often the seventh) day of life, peaked at 5 to 27

days, and whose maximum recorded SB levels ranged from 7 to 27 mg/dl. Again a more rapid decrease in SB levels was confirmed when formula was introduced than when breast feeding alone was continued. Eleven of these 20 infants were considered to have had "physiologic jaundice," which either receded partially, or disappeared before the onset of more severe jaundice. In infants who continued to be breast fed, jaundice began to regress at about 20 days, and disappeared by 30–60 days of age, despite continued inhibitory activity in the breast milk.

Although the original investigations implicated a progestational steroid (3- α , 20 β —pregnane-diol) in breast milk as the inhibitory substance, more recent reports have shown unsaturated free fatty acids produced by high lipase activity in some women's breast milk to inhibit glucuronyl transferase.¹³

Arthur et al¹⁴ reported 3 additional cases of prolonged jaundice associated with high levels of inhibitory activity in the breast milk consumed by these infants but were unable to show any correlation between SB levels at six days of age in 28 BMF infants (maximum SB level, <8 mg/dl) and inhibitory activity in their mother's breast milk, despite a trend toward higher SB levels in BMF infants at both three and six days of age. This suggests a different etiology for prolonged versus early accentuation of jaundice in BMF infants.

As early as 1964, Lewi et al¹⁵ in the French literature, compared fifth day SB levels in BMF and FF infants, and unable to find a significant difference, concluded that the inhibitory factor described by Arias, although perhaps important in prolonged jaundice, seemed to play a negligi-

ble role in the production of jaundice during the first week of life.

In 1965 Stiehm and Ryan⁴ reported prolonged jaundice associated with breast feeding in 8 infants in whom maximum SB levels of 7–29.8 mg/dl were recorded at seven to 27 days of age (similar to the 20 infants reported by Gartner and Arias¹²). In half of these infants, jaundice was first noted after the first week of life. These authors further conducted a retrospective review of infants who had had at least one SB level determination during their neonatal hospitalization, and identified a disproportionate number of BMF infants among the 117 (2.7%) with unexplained jaundice. This was due almost entirely to 20 infants (0.5% of the total) with maximum SB level, >15 mg/dl, among whom 14 were breast fed. Maximum SB level was noted on day 4, but the authors note that duration of jaundice (and conceivably maximum level of SB) was uncertain since many infants were discharged while still jaundiced. The incidence of SB level, >15 mg/dl among BMF infants in this study, was still only 0.73% compared to 4.4% in the present study.

In 1973 Dahms et al² reported the results of a prospective study of 199 newborns designed to determine whether breast feeding and jaundice were related during the first week of life and whether SB levels were influenced by demand or scheduled feedings. Although their results indicate a definite trend toward higher mean SB levels at 48 and 72 hours, and higher maximum SB levels in BMF infants, the differences were not statistically significant ($P > 0.3$). Demand-fed BMF infants (who ingested only breast milk and lost the most weight) had the highest mean SB levels, followed by schedule-fed BMF infants (who received two formula supplements per day), and then schedule-fed FF infants. Demand-fed FF infants (who ingested the most formula and lost the least weight) had the lowest SB levels in the study. Although weight loss among demand-fed BMF infants was significantly greater, there was no relationship between weight loss and SB level. In these authors' comparison of the percentage of BMF and FF infants with SB level, >10 mg/dl, schedule- and demand-fed infants were combined, and this may have negated any significant difference that might have been present, since their own data confirm the trend toward lower SB levels that supplementation with formula can produce.

Winfield and MacFaul⁶, in an effort to deter-

mine an incidence for prolonged "breast milk jaundice," reported that 2.4% of all BMF infants during a six-month period had visible jaundice (SB level, 7–11.6 mg/dl) lasting at least three weeks. Again, the onset (day 2–5), and peak (day 3 to 14) overlap with physiologic jaundice.

In 1979 Wood et al¹⁶ obtained plasma bilirubin levels on 690 infants at about the sixth day of life, and analyzed these in relationship to many factors that might affect the presence of jaundice. Three factors—epidural analgesia, breast feeding, and poor weight recovery—showed highly significant associations with jaundice, although no explanation for the association with epidural analgesia was identified.

DeAngelis et al⁷ in 1980 reported a retrospective two-year study of 251 infants in which 82% were breast fed. They reported a 25.7% incidence of SB >10 mg/dl among BMF infants compared to 8.9% of FF infants ($P < 0.01$). Although they detected no significant difference in phototherapy for SB level, >15 mg/dl between BMF (6.8%) and FF (2.2%) infants, the authors note that an additional 10 BMF infants were taken off breast milk at SB level of 12 mg/dl, only one of whom eventually required phototherapy. In contrast, 13 of 43 BMF infants who continued to breast feed eventually had phototherapy. The authors suggest, therefore, that phototherapy should be used only if a decrease in SB to an acceptable level does not follow temporary cessation of breast feeding at 3–4 mg/dl below the level felt to necessitate phototherapy. Although advocates of breast feeding might argue that such interruption may interfere with the establishment of successful breast feeding, the high rate of jaundice in the infants of nursing mothers in this study would suggest otherwise.

DeAngelis et al⁷ observed a correlation between the average number of sunshine hours per month in Madison, Wisconsin, and the percent of infants with SB level, >10 mg/dl (12% of infants born April through August, and 31% of infants born September through March). Although an attempt was made in the present study to correlate monthly sunshine hours in Cleveland with SB level, >10 mg/dl, the consistently low number of sunshine hours during the winter months in Cleveland made any correlation impossible. However, the possibility of vitamin D interaction with lipase activity in breast milk has not been explored.

Verronen et al,¹⁷ in 1980, also reported a high

incidence of both SB level, >12 mg/dl (33%), and a high incidence of phototherapy (10%) in BMF infants, but the criteria for phototherapy were not noted.

Saigal et al¹ recently reported results of their prospective study comparing SB levels, weight loss, and phototherapy during the first week of life in 176 BMF and 164 FF infants. Despite significant differences in both SB level and weight loss on each day tested, the authors found no correlation between cumulative weight loss on day 3 and SB level in either BMF or FF infants. The controlled use of formula supplementation for BMF infants (especially for those with higher SB level or weight loss) may again bias these results. The authors also note that phototherapy was used in 17 (9.6%) of the BMF, and only three (1.8%) of the FF infants, but, that in more than one third of cases, SB level was <10 mg/dl at the onset of phototherapy. Of those infants whose SB level peaked at ≥ 12 mg/dl, there was a significant difference in the percent of BMF versus FF infants (26% versus 7%, $P < 0.001$).

Conclusion

In the 20 years since the first reported cases of prolonged unexplained jaundice in breast milk fed infants, the term "breast milk jaundice" has been loosely applied to what may now be more appropriately recognized as two separate disorders.

The clearly documented, but rather infrequently occurring prolonged jaundice in certain breast milk fed infants appears to be caused by an inhibitor of glucuronyl transferase in the breast milk consumed by these infants, and according to the available literature, probably has an incidence of about 2% in all infants fed breast milk exclusively. This jaundice has its onset at the end of the first week of life and should perhaps be designated "late breast milk jaundice."

More difficult to document, but more prevalent, is the exaggerated physiologic jaundice seen in a significant minority of breast-milk-fed infants who also experience increased weight loss. This jaundice occurs during the first week of life and could more appropriately be designated "early breast milk jaundice." Unfortunately, many reported cases undoubtedly represent an overlap of these two entities.

Further studies are necessary to determine whether the early and late forms of breast milk jaundice represent a qualitatively, or simply a

quantitatively different population. A large group of prospectively enrolled infants, followed for a prolonged period of time with frequent SB level determinations, would be necessary to make this distinction.

Acknowledgments

We wish to thank James P. Orlowski, M.D., for his constructive comments.

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