Is Breastfeeding Really Favoring Early Neonatal Jaundice?

Giovanna Bertini, MD; Carlo Dani, MD; Michele Tronchin, PhD; and Firmino F. Rubaltelli, MD

Objective. The purpose of this study was to evaluate the development of significant hyperbilirubinemia in a large unselected newborn population in a metropolitan area with particular attention to the relationship between type of feeding and incidence of neonatal jaundice in the first week of life.

Study Design. A population of 2174 infants with gestational age ≥37 weeks was prospectively investigated during the first days of life. Total serum bilirubin determinations were performed on infants with jaundice. The following variables were studied: type of feeding, method of delivery, weight loss after birth in relationship to the type of feeding, and maternal and neonatal risk factors for jaundice. Statistical analyses were performed using the z test for parametric variables and the t test for nonparametric variables. In addition, the multiple logistic regression allows for the estimation of the role of the individual characteristics in the development of hyperbilirubinemia. Data concerning serum bilirubin peak distribution in jaundiced newborns were analyzed using a single and a double Gaussian best fit at least squares. The t test was performed to compare 2 values (high and low) of the serum bilirubin peak in breastfed and supplementary-fed infants with those in bottle-fed infants.

Results. The maximal serum bilirubin concentration exceeded 12.9 mg/dL (221 μmol/L) in 112 infants (5.1%). The study demonstrated a statistically significant positive correlation between patients with a total serum bilirubin concentration >12.9 mg/dL (221 μmol/L) and supplementary feeding; oppositely, breastfed neonates did not present a higher frequency of significant hyperbilirubinemia in the first days of life. However, best Gaussian fitting of our data suggests that a small subpopulation of breastfed infants have a higher serum bilirubin peak than do bottle-fed infants.

Newborns with significant hyperbilirubinemia underwent a greater weight loss after birth compared with the overall studied population, and infants given mixed feeding lost more weight than breastfed and formula-fed newborns, indicating that formula has been administered in neonates who had a weight loss beyond a pre-determined percentage of birth weight. Significant hyperbilirubinemia was also strongly associated with delivery by vacuum extractor, some perinatal complications (cephalohematoma, positive Coombs’ test, and blood group systems of A, AB, B, and O [ABO] incompatibility) and Asian origin. Multiple logistic regression analysis shows that supplementary feeding, weight loss percentage, ABO incompatibility, and vacuum extraction significantly increase the risk of jaundice, while only cesarean section decreases the risk.

Conclusion. The present study confirms the important role of fasting in the pathogenesis of neonatal hyperbilirubinemia, although breastfeeding per se does not seem related to the increased frequency of neonatal jaundice but to the higher bilirubin level in a very small subgroup of infants with jaundice. In fact, in the breastfed infants, there is a small subpopulation with higher serum bilirubin levels. These infants, when starved and/or dehydrated, could probably be at high risk of bilirubin encephalopathy. Pediatrics 2001;107(3).

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Newborn infant, hyperbilirubinemia, neonatal jaundice.

ABBREVIATIONS. ABO, blood group systems of A, AB, B, and O; TBS, total serum bilirubin.

Neonatal jaundice remains the most common and, perhaps, the most vexing problem in full-term infants during the immediate postnatal period. Despite the numerous articles published on this subject, many aspects of neonatal hyperbilirubinemia remain unexplained.1–7 In particular, there is an important debate on the role of breastfeeding versus formula feeding in determining the number of infants with significant hyperbilirubinemia as well as influencing the peak serum bilirubin concentration1–7 in the first days of life.

The aim of this study was to investigate the occurrence of significant hyperbilirubinemia in a large unselected population of full-term newborns in a metropolitan area.

METHODS

A population of 2174 newborn infants with gestational age ≥37 weeks consecutively born in the Department of Obstetrics and Gynecology of the University of Florence Hospital between November 15, 1997 and November 14, 1998 was prospectively studied. Gestational age was determined according to last menstrual period. No participants presented severe asphyxia, infections, abnormal direct serum bilirubin values, malformations, or other pathologic conditions. All infants admitted to the study were in a continuous rooming-in setting, meaning that newborns were in their cots near their mothers’ beds.

Mothers had their blood group typed and all newborns had blood group determination and the Coombs’ test performed on cord blood. Total bilirubinemia in infants with jaundice was measured by direct spectrophotometry of the serum in a microhematocrit tube (using the Elmed Ginevri bilirubinometer). A bilirubin level >12.9 mg/dL (221 μmol/L) was considered significant. Infants with bilirubin level >12.9 mg/dL (221 μmol/L) at 24 hours of life and with bilirubin level >17 mg/dL (291 μmol/L) in the days that followed were candidates for phototherapy according to the guidelines of the Italian Society of Neonatology.8 Serum bili-
rubin levels were monitored in infants with jaundice twice daily in subsequent days until a steady decrease was observed. The variables evaluated in this study are the following: type of feeding (breastfeeding, formula feeding, or supplementary feeding); method of delivery (vaginal delivery, cesarean section, or vacuum extractor); weight loss after birth in relationship to type of feeding; and maternal and neonatal risk factors for jaundice development (maternal diabetes and hypertension, neonatal gender, origin and gestational age, positive Coombs’ test, blood group systems of A, AB, B, and O [ABO] incompatibility, and the presence of cephalohematoma).

Breastfeeding refers to infants who were exclusively breastfed. The mothers started nursing in the delivery room and breastfed on their infants’ demand every 1 to 3 hours (generally 10 minutes on each breast) with no supplementation of water or formula at any time. Pacifiers were forbidden and the number offeedings was between 6 and 12 per day.

Supplementary feeding refers to infants who were breastfed and received additional formula supplements. In our nursery, the attending neonatologist commonly prescribed supplementary formula if birth weight was <2500 g or if weight loss after birth was significant (>4% after 24 hours or >8% after 48 hours or >10% after 72 hours). No water or glucose water was administered at any time.

Formula feeding refers to infants who were exclusively bottle-fed because their mothers presented some pathologic conditions that represented contraindications to breastfeeding or declined to breastfeed.

Most infants were discharged after 72 hours of life. Newborns who were born by cesarean section, were jaundiced, or presented significant weight loss remained in the hospital longer. The range of length of stay was 83.43 ± 53.03 hours.

Statistical analyses were performed using the t test for parametric variables and the χ test for nonparametric variables. A P value <.05 was considered statistically significant. In addition, the multiple logistic regression allows us to estimate the role of the individual characteristics in the development of hyperbilirubinemia; a value of t = 1.96 (P = .05) was chosen as the significant cutoff value. Data concerning serum bilirubin peak distribution in jaundiced newborns were analyzed using a single and a double Gaussian best fit at least squares. The t test was performed to compare 2 values (high and low) of serum bilirubin peak in breastfed and supplementary-fed infants with those in bottle-fed infants.

RESULTS

The characteristics of the study group are shown in Table 1. During their hospital stay, 528 infants (24.3% of the 2174 studied) were recognized to be clinically jaundiced and required bilirubin determination, of whom there were 43% on the second day of life and 46% on the third day of life. Among these, only 112 (5.1%) had total serum bilirubin (TSB) >12.9 mg/dL or >221 μmol/L (significant hyperbilirubinemia). A serum bilirubin peak >12.9 mg/dL occurred more frequently on the third and fourth days of life. A statistically significant positive correlation was found between TSB >12.9 mg/dL (221 μmol/L) and supplementary feeding (P < .001), delivery by vacuum extractor (P < .001), perinatal complications (cephalohematoma, positive Coombs’ test, and ABO incompatibility; P < .001), and Asian origin (P < .001). Breastfeeding showed a negative correlation with TSB >12.9 mg/dL (P < .001) (Table 2). Newborns with TSB >12.9 mg/dL (221 μmol/L) underwent a greater weight loss after 72 hours of life than did the overall studied population (8.0% vs 6.4%; P < .001; Table 3). Infants given mixed feeding lost more weight than did breastfed and formula-fed newborns. The additional multiple logistic regression analysis shows a positive, statistically significant correlation between TSB >12.9 and supplementary feeding, delivery by vacuum extractor, ABO incompatibility, and weight loss percentage after birth. A negative, statistically significant correlation was observed between TSB >12.9 and cesarean section (Table 4). In this type of analysis, neonatal characteristics, just as the appearance of cephalohematoma, a positive Coombs’ test, and Asian origin, have not proved to be statistically significant: probably, the number of infants with these disorders are too few to have sufficient statistical power. Best Gaussian fitting of our data suggests that 2 subpopulations are present among breastfed and supplementary-fed infants with jaundice of unknown origin: a subpopulation with a low serum bilirubin peak and a subpopulation with a high serum bilirubin peak. In bottle-fed newborns, only 1 population seems present. The subgroups of breastfed and supplementary-fed infants have a higher second serum bilirubin peak compared with bottle-fed newborns (14.4 ± 2.9 mg/dL, 14.1 ± 3.1 mg/dL vs 11.0 ± 4.5 mg/dL; P < .05; data are shown in Fig 1).

DISCUSSION

This epidemiologic study investigated the effects of different variables on nonphysiologic hyperbilirubinemia in a large cohort of full-term newborn infants in the first week of life. Several authors have reported an increase in the frequency of readily visible jaundice in the last 25 years, probably secondary to breastfeeding encouragement in the same period.2,3 In our study, the incidence of clinically evident jaundice resulted similar to the National Collaborative Perinatal Project conducted from 1959 to 1966 (24.3% vs 26.3%)4; at that time, only 22% to 23% of mothers in the United States were breastfeeding their infants. Because 73.4% of our infants were breastfed, our findings seem to suggest that the frequency of infants with clinically evident jaundice is not related to the type of feeding in our study population.

During the first week of life, the incidence of nonphysiologic hyperbilirubinemia (TSB >10–12.9 mg/dL or 171–221 μmol/L) in full-term newborns was reported in different studies to be between 4.8% and 15.5%.1,3,5; in our study population the incidence of significant hyperbilirubinemia is low (5.15%). Our findings confirm the strong association be-

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**TABLE 1.** Characteristics of the Study Group (Mean Values ± Standard Deviation or Percentage)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of Neonates Studied</th>
<th>Mean Value ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (g)</td>
<td>2174</td>
<td>3290.12 ± 162.65</td>
</tr>
<tr>
<td>Birth weight (g):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>1143</td>
<td>3289.82 ± 162.65</td>
</tr>
<tr>
<td>Females</td>
<td>1031</td>
<td>3291.20 ± 162.65</td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td></td>
<td>39.2 ± 1.7</td>
</tr>
<tr>
<td>Vaginal delivery</td>
<td></td>
<td>1691 (77.8%)</td>
</tr>
<tr>
<td>Cesarean section</td>
<td></td>
<td>426 (19.6%)</td>
</tr>
<tr>
<td>Vacuum extractor</td>
<td></td>
<td>57 (2.6%)</td>
</tr>
<tr>
<td>Breastfed</td>
<td></td>
<td>1595 (73.4%)</td>
</tr>
<tr>
<td>Formula-fed</td>
<td></td>
<td>101 (4.6%)</td>
</tr>
<tr>
<td>Supplementary feeding</td>
<td></td>
<td>478 (22%)</td>
</tr>
<tr>
<td>European origin</td>
<td></td>
<td>1997 (91.8%)</td>
</tr>
<tr>
<td>Asian origin</td>
<td></td>
<td>102 (4.8%)</td>
</tr>
<tr>
<td>African origin</td>
<td></td>
<td>18 (0.8%)</td>
</tr>
<tr>
<td>Mediterranean origin</td>
<td></td>
<td>39 (1.8%)</td>
</tr>
<tr>
<td>South American origin</td>
<td></td>
<td>18 (0.8%)</td>
</tr>
</tbody>
</table>
ing and significant hyperbilirubinemia, but other re-
ported a striking association between breastfeed-
ning in the delivery room, they are in a rooming-in
setting, and are breastfed on demand. Infants receive
supplementary feeding only when adequate breast-
feeding has failed. In fact, breastfed infants, com-
pared with newborns given supplementary feeding,
had lower weight loss after birth than did the overall
studied population. Moreover, jaundice was first evi-
ent in 42% of infants on the second day and in 55%
on the third day when the percentage of infants with
a maximum weight loss was 52% and 45%, respec-
tively. Multiple regression logistic analysis shows a
statistically positive correlation between TSB >12.9
cd/L (221 µmol/L) and weight loss percentage after birth. These data confirm that the development
of neonatal jaundice is not associated with breast-
feeding per se but rather with increased weight loss
after birth subsequent to fasting, suggesting the im-
portant role of caloric intake in the regulation of
serum bilirubin. In fact, Osborn et al1 as well as
Maisels et al4 found that jaundiced infants did lose
more weight than control infants. A relationship be-
tween fasting and hyperbilirubinemia has been pre-
viously reported both in adults and animals.13,14 The
effect of caloric restriction on serum bilirubin was
first noted by Gilbert and Hershi15 in 1906. Later on,
Barrett16 and Felsher et al17 showed that fasting
causes a significant elevation of unconjugated biliru-
bin. Bloomer et al13 by injecting bilirubin H3 into
normal adult volunteers and in patients with Gil-
bert’s syndrome, demonstrated that the decrease in
clearance was the result of reduced hepatic ability to
extract bilirubin from the blood. Moreover, in the
Cooperative National Institute of Child Health and
Human Development phototherapy, Wu et al18 found that infants receiving <90 calories/kg/24
hours had significantly higher peaks in bilirubin con-
centrations than did those fed >90 calories/kg/24
hours, and phototherapy was much less effective
when calcific and fluid intake was low. In contrast,
measurements of pulmonary excretion of carbon
monoxide (an index of bilirubin production) showed
no effect of caloric deprivation on bilirubin produc-
tion.19 A recent article by Gartner et al20 investigated
the effect of fasting in rats using a technique that

### TABLE 2. Neonatal Hyperbilirubinemia in Relation to Selected Neonatal and Maternal Characteristics: A Comparison Between All Neonates and Those With TSB >12.9

<table>
<thead>
<tr>
<th>Number</th>
<th>Infants</th>
<th>Infants With TSB &gt;12.9 mg/dL (221 µmol/L)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates studied</td>
<td>2174</td>
<td>112</td>
<td>5.15</td>
</tr>
<tr>
<td>Breastfed</td>
<td>1595</td>
<td>43</td>
<td>2.7</td>
</tr>
<tr>
<td>Formula-fed</td>
<td>101</td>
<td>6</td>
<td>0.9</td>
</tr>
<tr>
<td>Supplementary feeding</td>
<td>478</td>
<td>63</td>
<td>13.1</td>
</tr>
<tr>
<td>Vaginal delivery</td>
<td>1691</td>
<td>82</td>
<td>4.8</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>426</td>
<td>20</td>
<td>4.7</td>
</tr>
<tr>
<td>Vacuum extractor</td>
<td>57</td>
<td>10</td>
<td>17.5</td>
</tr>
<tr>
<td>Maternal diabetes</td>
<td>136</td>
<td>9</td>
<td>6.6</td>
</tr>
<tr>
<td>Maternal hypertension</td>
<td>37</td>
<td>2</td>
<td>5.4</td>
</tr>
<tr>
<td>Cephalhematoma</td>
<td>24</td>
<td>7</td>
<td>29.1</td>
</tr>
<tr>
<td>Positive Coombs’ test</td>
<td>73</td>
<td>17</td>
<td>23.2</td>
</tr>
<tr>
<td>ABO incompatibility</td>
<td>293</td>
<td>38</td>
<td>13.0</td>
</tr>
<tr>
<td>Males</td>
<td>1143</td>
<td>60</td>
<td>5.2</td>
</tr>
<tr>
<td>Females</td>
<td>1031</td>
<td>52</td>
<td>5.0</td>
</tr>
<tr>
<td>European origin</td>
<td>1997</td>
<td>92</td>
<td>4.6</td>
</tr>
<tr>
<td>Asian origin</td>
<td>102</td>
<td>16</td>
<td>15.6</td>
</tr>
<tr>
<td>African origin</td>
<td>18</td>
<td>1</td>
<td>5.5</td>
</tr>
<tr>
<td>South American origin</td>
<td>18</td>
<td>1</td>
<td>5.5</td>
</tr>
<tr>
<td>Mediterranean origin</td>
<td>39</td>
<td>2</td>
<td>5.1</td>
</tr>
</tbody>
</table>

### TABLE 3. Weight Loss After Birth and Neonatal Hyperbilirubinemia

<table>
<thead>
<tr>
<th>Weight Loss After 72 Hour of Life (Grams)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All infants studied</td>
<td>214.63 ± 146</td>
</tr>
<tr>
<td>Infants with TSB &gt;12.9 mg/dL</td>
<td>264.49 ± 74</td>
</tr>
<tr>
<td>Supplementary-fed</td>
<td>266 ± 150</td>
</tr>
<tr>
<td>Breastfed infants</td>
<td>200.33 ± 145</td>
</tr>
<tr>
<td>Formula-fed infants</td>
<td>207.2 ± 70</td>
</tr>
</tbody>
</table>

- P < .001 among infants with TSB >12.9 mg/dL and all infants studied.
- P < .01 among supplementary and breastfed infants.
- P < .01 among supplementary and formula-fed infants.
enables the assessment of the hepatic handling of unconjugated bilirubin independent of nonhepatic factors. This study clearly documents that enhanced enterohepatic circulation of bilirubin, not altered intrinsic hepatic transport, is a major factor in the pathogenesis of fasting-induced hyperbilirubinemia. In our study, best Gaussian fitting of data concerning serum bilirubin peak distribution in breastfed newborns shows that there is a subpopulation with a high serum bilirubin peak, which is not present in bottle-fed infants. However, this subpopulation seems to be very large among infants with mixed feeding who were the infants with the higher weight loss (Fig 1). It is worthwhile to underline that the occurrence of a decreased incidence of significant jaundice in breastfed infants is related to the first days of life (early jaundice). The incidence of late jaundice, whose onset generally occurs on the fourth day and lasts \( \sim 9 \) weeks having a peak at 5 to 15 days, was not studied in our population.

It is well known that genetic and environmental factors influence neonatal jaundice. According to previous data in literature, the method of delivery also influences serum bilirubin concentration\(^2\), and this report found that cesarean sections preserve newborn infants by the development of neonatal hyperbilirubinemia. There are some possible explanations. The infants born by emergency cesarean section are stressed before birth and, therefore, induce conjugating enzymes before delivery. Moreover, Osborn et al\(^2\) have suggested a probable association between delivery by cesarean section and method of feeding. In their hospital, because women who underwent cesarean section breastfed infrequently during the newborn’s first 48 hours of life, these infants, unlike other breastfed infants, were supplemented with formula until nursing was well established. Nevertheless, our setting after cesarean section provides for supplementation with formula only at the mother’s request or if weight loss after birth is significant. Yamauchi and Yamanouchi\(^21\) demonstrated that from day 1 to day 7 of life, transcutaneous bilirubin measurement in infants born by cesarean section was significantly lower than those of infants born vaginally, likely because of less placental transfusion in infants born by cesarean section. In addition, a strong association was found between significant hyperbilirubinemia in the first week and delivery by means of vacuum extractor; this is probably because of the development of hemorrhaging consequent to this method of delivery as has been observed in the past,\(^22\) but currently it is not widely recognized. Ethnic differences in the incidence of neonatal jaundice are significant\(^9,23\) and the present investigation confirms that race plays an im-

### TABLE 4. Multiple Logistic Regression Analysis for Characteristics Potentially Associated With Neonatal Hyperbilirubinemia

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
<th>Standard Error</th>
<th>t</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>-0.02069183018</td>
<td>0.049716455409</td>
<td>-0.4161968</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>-0.15284435863</td>
<td>0.06037950031</td>
<td>-2.5313949*</td>
</tr>
<tr>
<td>Vacuum extractor</td>
<td>0.30723170710</td>
<td>0.11652928879</td>
<td>2.6365192*</td>
</tr>
<tr>
<td>Birth weight</td>
<td>0.00004338651</td>
<td>0.00006470326</td>
<td>0.26705460</td>
</tr>
<tr>
<td>Gestational age</td>
<td>-0.00109275960</td>
<td>0.00059995650</td>
<td>-0.2061827</td>
</tr>
<tr>
<td>Supplementary feeding</td>
<td>0.30536674845</td>
<td>0.0504706766</td>
<td>5.5473754*</td>
</tr>
<tr>
<td>Formula feeding</td>
<td>0.13541467312</td>
<td>0.10814570679</td>
<td>1.2521518</td>
</tr>
<tr>
<td>ABO incompatibility</td>
<td>0.14240808203</td>
<td>0.05890298857</td>
<td>2.4340811*</td>
</tr>
<tr>
<td>Maternal hypertension</td>
<td>0.31065208999</td>
<td>0.19735173451</td>
<td>1.5741035</td>
</tr>
<tr>
<td>Maternal diabetes</td>
<td>0.21423038422</td>
<td>0.15274667994</td>
<td>1.4025207</td>
</tr>
<tr>
<td>Weight loss percentage</td>
<td>0.000044801641</td>
<td>0.00017684607</td>
<td>2.5333693*</td>
</tr>
</tbody>
</table>

* \( P < .05 \).
portant role in determining neonatal hyperbiliru-
binemia; 15.6% of Asian newborn infants compared
with 5.1% of the total population (91.8% European
newborns) showed a TSB >12.9 mg/dL (221
μmol/L; P < .001). Recently, Akaba et al suggested
that the high incidence of neonatal hyperbiliru-
binemia in Japanese, Korean, and Chinese populations
is associated with high frequency of the Gly71Arg mutation (missense mutation) of the bili-
rubin uridine diphosphate-glucuronosyltransferase
gene. Our data on the effect of gestational age do not
agree with those found by others authors, but our population was composed of newborn infants
with ≥39 weeks of gestational age (73%). Even if
other variables also play a role in hyperbilirubinemia
of full-term infants, breastfeeding failure and the
lack of breastfeeding are major factors in the path-
genesis of neonatal jaundice.

CONCLUSION

The present study confirms the important role of
fasting in the pathogenesis of neonatal hyperbiliru-
binemia, although breastfeeding per se does not
seem related to the increased frequency of neonatal
jaundice in the first days of life, but rather to the
higher bilirubin level in a very small subpopulation
of infants with jaundice. These infants, when starved
and/or dehydrated, could probably be at high risk of
bilirubin encephalopathy, especially after discharge
from the hospital when careful follow-up is lacking.
Among other well-known conditions favoring neo-
natal jaundice, it must be emphasized that infants
born by vacuum extraction are at risk of exaggerated
neonatal jaundice.

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Buthani of Pennsylvania Hospital (Philadelphia, PA) for review-
ing the manuscript and for their suggestions.

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859–861
mutation of the bilirubin uridine diphosphate-glucuronosyltransferase
gene: a common missense mutation among Japanese, Koreans and
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