Reduced Risk of Neonatal Respiratory Infections Among Breastfed Girls but Not Boys

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ABSTRACT. ***Objective.*** **The effect of breastfeeding on community-acquired neonatal infections has not been well studied, although the neonatal period is one of special vulnerability to infectious pathogens. Respiratory tract infections are the neonatal infection most commonly diagnosed after nursery discharge. We therefore chose respiratory tract infections diagnosed after nursery discharge as representative of neonatal community-acquired infection and studied the impact of breastfeeding on this neonatal infection syndrome.**

Methods. **An unmatched nested case-control study was performed within a previously defined study cohort of 13 224 mother-infant pairs delivering between October 1, 1990, and March 31, 1998. Infants who were delivered at < 37 weeks' gestation were excluded. Neonatal respiratory tract infections were defined using modified National Nosocomial Infections Surveillance System criteria and were included in the case series when diagnosed after nursery discharge and at age ≤30 days. Infant feeding status during the first month of life was ascertained using automated text search of electronic medical records and was categorized as exclusive breastfeeding, mixed feeding, or exclusive formula feeding.**

Results. **A total of 241 neonatal respiratory tract infections were found, and 1205 control subjects were selected. Compared with control subjects, case infants were more often born during the winter respiratory syncytial virus season (48% vs 33%), more likely to have a sibling present (70% vs 54%), and more likely to be a member of a socioeconomically at-risk family (24% vs 18%). Case patients were less likely to be exclusively breastfed (38% vs 44%) and equally likely to be exposed to mixed feeding (35% vs 34%) relative to control subjects. When compared with formula feeding only, the odds ratio (OR) of exclusive breastfeeding was 0.70 (95% confidence interval [CI]: 0.49–0.99) and that of mixed feeding was 0.83 (95% CI: 0.58–1.2). However, when stratified by infant sex, the inverse association between breastfeeding and risk of neonatal respiratory tract infection was confined to neonatal girls, for whom the unadjusted ORs associated with breastfeeding only and mixed feeding were 0.5 (95% CI: 0.29–0.78) and 0.6 (95% CI: 0.35–0.93), respectively. There was no meaningful association between breastfeeding and risk of neonatal respiratory tract infection among neonatal boys, for whom the unadjusted ORs associated with breastfeeding only and mixed feeding were 1.1 (95% CI: 0.63–1.8) and 1.3 (95% CI: 0.74–2.1), respectively. After adjustment for year of birth, season of birth, siblings, and socioeconomic status, both exclusive breastfeeding and mixed feeding remained protective among girls, with ORs of 0.5 (0.29–0.78) and 0.6 (0.34–0.93), respectively. The corresponding ORs for boys were 1.1 (0.64–2.0) and 1.4 (0.78–2.4).**

Conclusions. **Breastfeeding was inversely associated with reduced risk of neonatal respiratory tract infections in girls but not in boys. Breastfeeding may confer protection against some community-acquired infections as early as the first month of life.** ***Pediatrics*** **2003;112:e303–e307. URL: http://www.pediatrics.org/cgi/content/full/112/4/e303;** ***neonatal respiratory tract infections, breastfeeding, girls.***

ABBREVIATIONS. BWH, Brigham and Women's Hospital; HMO, health maintenance organization; HPHC, Harvard Pilgrim Health Care; HVMA, Harvard Vanguard Medical Associates; NNIS, National Nosocomial Infections Surveillance System; OR, odds ratio; CI, confidence interval.

The protective effects of breastfeeding on the risk of infections during infancy and early childhood have been well described.[1] Recent work has focused on the duration of exclusive breastfeeding necessary to confer protection against infection during infancy.[2] However, the question of how early in life protection against infection conferred by breastfeeding begins remains an open question. Specifically, what is the impact of breastfeeding on neonatal infections? The neonatal host is well recognized as being especially vulnerable to infection acquired vertically, nosocomially, and from the community.[3] Breastfeeding could potentially confer protection against pathogens transmitted via the last 2 routes. A prophylactic role for breast milk in the prevention of necrotizing enterocolitis[4] and neonatal sepsis[5] among high-risk infants in the neonatal intensive care unit has been demonstrated, but there is little published evidence supporting the role of breastfeeding in the prevention of community-acquired neonatal infections.

Respiratory tract infections are the neonatal infection most commonly diagnosed after nursery dis-

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charge,[6] and they are typically not caused by congenital structural anomalies, as might be the case for other syndromes such as urinary tract infections. We therefore chose respiratory tract infections diagnosed after nursery discharge as representative of neonatal community-acquired infection and studied the impact of breastfeeding on this neonatal infection syndrome.

METHODS

Study Population

As previously described,[6] the study population consisted of all infants who were delivered at the Brigham and Women's Hospital (BWH) in Boston, Massachusetts, between October 1, 1990, and March 31, 1998, and whose mothers were members of a large health maintenance organization (HMO), Harvard Pilgrim Health Care (HPHC), and who were cared for by Harvard Vanguard Medical Associates (HVMA; the staff model division of HPHC at that time) during the first 30 days of life. Excluded from the cohort were infants who could not be paired with their mothers, for whom discrepancies in identifying data existed, or for whom complete medical records were not available. This cohort was developed for a study of the impact of intrapartum antibiotics on neonatal infections.[7] For the present study, we also excluded all infants who were delivered at <37 weeks' gestational age.

Case Definition

Case patients were defined as full-term infants who had upper respiratory tract infections and nonpneumonia lower respiratory tract infections diagnosed after hospital nursery discharge during the first 30 days of life. These respiratory tract infections were defined using modified National Nosocomial Infections Surveillance System (NNIS) criteria.[8] We combined these into 1 category, comprising upper respiratory tract infection (NNIS code UR) and lower respiratory tract infection, other than pneumonia (NNIS code BRON).

For the analyses presented here, we elected not to include cases of pneumonia, because pneumonia may have a spectrum of microbial causes different from nonpneumonia categories of respiratory tract infection. We hypothesized that bacterial pathogens and vertically transmitted pathogens such as *Chlamydia trachomatis* might be important causes of pneumonia. whereas nonpneumonia infections such as bronchiolitis would be largely viral in origin. Nevertheless, in separate analyses in which the 5 identified cases of pneumonia were included, our results were the same.

Identification of Case Patients and Control Subjects

Potential cases of infection were identified by screening the HMO's automated medical records and claims data for the presence of a diagnostic code suggestive of respiratory tract infection. These codes were COSTAR (Computer-Stored Ambulatory Record, Massachusetts General Hospital, Boston, MA) codes A117, E408, E410, E413, E414, E250, E257, E260, E261, G120, G121, G123, G270, G276, G363, G365, G992, and Y265, as well as *International Classification of Diseases, Ninth Revision* codes 430, 461, 462, 463, 464, 465, and 466 (with 4- and 5-digit subcategories as applicable). These codes were related to conditions both common and rare among neonates: viral illness, rhinitis, upper respiratory tract infection, coryza, sinusitis, pharyngitis, bronchitis, bronchiolitis, and pathogen-specific diagnoses. Outpatient and relevant hospital records were obtained for all infants with 1 or more of these codes. These records were then reviewed to verify the presence or absence of infection. For a set of 10 neonatal infection syndromes, including respiratory tract infections, we previously used patient-reported questionnaire data and chart review of a random sample of 100 infants to estimate that our screening method's sensitivity was 83%, as reported.[6]

Control subjects were unmatched and randomly selected at a 5:1 ratio from among noninfected members of the study cohort for this nested analysis. Preliminary analysis showed no large variations in the annual incidence of respiratory tract infections, and we chose to control for year of birth and season of birth in the analysis rather than by matching of control subjects. We estimated a total of 204 case patients and 1020 control subjects would be necessary to achieve a power of >80% for an odds ratio (OR) of 0.6 for exclusive breastfeeding relative to formula feeding alone.

Infants were categorized as either belonging or not belonging to a family that was socioeconomically at risk. Using HMO and 1990 US census data, at-risk families were defined as those meeting 1 or more of the following criteria: maternal age <22, enrollment of either mother or infant in the state Medicaid program, residence in a census tract with a median income <$25 000, or residence in a census tract with greater than one third of adults not having a high school diploma or equivalent by age 25. Using both hospital and HMO data, patients were categorized as non-Hispanic white, black, or other. Infants were categorized as likely to have siblings present if the mother had previously carried an infant to term (maternal parity >1) using both hospital and HMO data.

Infant Feeding Practice

Feeding practice was determined using a validated, automated text-searching method based on infants' electronic medical records, as described in greater detail elsewhere.[9] The method used was blind to case patient or control subject status. For the present analyses, infant hospital and health center encounters up to 45 days after birth were included, to ensure complete capture of follow-up visits routinely scheduled at 1 month (30 days). Coded and free-text fields in the medical records data were searched for >100 specific terms indicating either breastfeeding or formula feeding (eg, "BF," "brfeeding," "breastmilk," "Enfamil," "enf,").

Remarks regarding feeding practice were found in almost all clinical encounters at this early age. Infants for whom only breastfeeding terms appeared within 45 days of records were classified as exclusively breastfed, and infants with only formula-related terms were classified as exclusively formula-fed. Infants whose records contained both types of terms were classified as mixed feeders. The mixed feeding group thus includes breastfeeding infants who ever received supplementation during the ascertainment period and infants who weaned from breastfeeding during that time.

Statistical Analysis

SAS version 6.12 (SAS Institute, Cary, NC) was used for all analyses. Analyses were performed and statistical significance was tested using χ^2 tests, paired t tests, or nonparametric tests, such as the Wilcoxon rank sum test, as appropriate. All P values are 2-sided. Stratified analyses were performed using logistic regression. A logistic regression model including all candidate covariates was built, and covariates with $P > .05$ were then removed. These candidate variables were year of birth, maternal age, season of birth, siblings present, socioeconomic at risk status, and race. Variables that failed statistical criteria but that were of known importance (year of birth and socioeconomic status) were retained in the final model. Institutional Review Board approval for this study was obtained from both BWH and HPHC.

RESULTS

We identified 29 907 infants who were delivered by HMO members from October 1, 1990, to March 31, 1998, and followed in the HMO's staff model pediatric practice for at least 45 days after birth. Of these, 27 631 (92.4%) infants were able to be linked with their mothers' HMO data, had no inconsistencies in identifying data, and had full automated data available. Of these mother-infant pairs, 13 224 were identified as having been delivered at BWH and constituted the original study cohort. Of those infants, 12 420 were born at a gestational age ≥37 weeks and were included in the population for the current study.

Diagnostic screening codes indicated potential neonatal respiratory tract infection in 933 infants. We were able to obtain and review 923 (99%) charts to confirm the presence or absence of infection. For 241 infants, nonpneumonia respiratory tract infections were confirmed, and these cases are included in the present analysis. The median age at time of diagnosis was 22 days. Five pneumonias were also diagnosed after nursery discharge and were not included in this study. We randomly selected 1205 control subjects from the study population.

The descriptive characteristics of case patients and control subjects are summarized in Table 1. Compared with control subjects, case infants were more often born during the winter respiratory syncytial virus season, more likely to have a sibling present, and more likely to be a member of a socioeconomically at-risk family. As shown in Table 1, case patients were less likely to be exclusively breastfed (38% vs 44%) and equally likely to be exposed to mixed feeding (35% vs 34%) relative to control subjects. When compared with formula feeding only, the OR of exclusive breastfeeding was 0.70 (95% confidence interval [CI]: 0.49–0.99) and that of mixed feeding was 0.83 (95% CI: 0.58–1.2). However, when stratified by infant sex, the inverse association between breastfeeding and risk of neonatal respiratory tract infection was confined to neonatal girls (Table 2). There was no meaningful association between breastfeeding and risk of neonatal respiratory tract infection among neonatal boys (Table 2).

Potential confounders assessed were birth weight, year of birth, season of birth, presence of siblings, socioeconomic status, maternal age, race, and infant sex. The associations between these potential confounders and breastfeeding among control neonates are given in Table 3. Although birth weight, year of birth, maternal age, socioeconomically at-risk family, and race all were significantly associated with breastfeeding, only at-risk status was also significantly associated with risk of neonatal respiratory tract infection. The OR for the association between socioeconomic at-risk status and neonatal respiratory tract infection was 1.6 (95% CI: 1.1–2.4). No evidence for effect modification by factors other than infant sex was found. After controlling for year of birth, season of birth, presence of siblings, and socioeconomic status, the inverse association between breastfeeding and risk of neonatal respiratory tract infection remained significant among neonatal girls, with no significant association found for neonatal boys (Table 2).

DISCUSSION

Breastfeeding was inversely associated with neonatal respiratory tract infections among neonatal girls but not neonatal boys. We hypothesized that nonpneumonia respiratory tract infections diagnosed after nursery discharge among full-term infants were most likely contracted through exposure

TABLE 1. Descriptive Characteristics of Case Patients and Control Subjects

	Case Patients	Control Subjects	*P* Value
	n = 241 (%)	n = 1205 (%)	
Infant feeding practice			
Breastfeeding only	91 (38)	528 (44)	>.05 (NS)
Mixed feeding	85 (35)	415 (34)	
Formula only	65 (27)	262 (22)	
Sex			
Male	120 (50)	593 (49)	
Female	121 (50)	612 (51)	
Gestational age			
37–40 wk	163 (68)	835 (70)	>.05 (NS)
41+ wk	76 (32)	365 (30)	
Birth weight			
<2500 g	5 (2)	40 (3)	
>2500 g	236 (98)	1165 (97)	
Maternal age			
<20 y	11 (5)	29 (2)	>.05 (NS)
20–29 y	75 (31)	366 (30)	
30–39 y	148 (61)	753 (62)	
>40 y	6 (2)	57 (5)	
Year of birth			
1990–1994	130 (54)	727 (60)	
1995–1998	111 (46)	478 (40)	
Season of birth*			
RSV season (December–March)	115 (48)	396 (33)	.001
Non-RSV season (April–November)	126 (52)	809 (67)	
Presence of siblings			
Yes	169 (70)	646 (54)	.001
No	71 (30)	555 (46)	
At-risk family			
Yes	58 (24)	986 (18)	.03
No	183 (76)	219 (82)	
Race			
White	145 (60)	747 (63)	>.05 (NS)
Black	63 (26)	282 (24)	
Other	32 (13)	155 (13)	
Route of delivery			
Vaginal	200 (83)	944 (78)	>.05 (NS)
Cesarean section	41 (17)	261 (22)	

NS indicates not significant, RSV, respiratory syncytial virus.

TABLE 2. Breastfeeding and Neonatal Respiratory Tract Infections

	Case Patients (*N* [%])	Control Subjects (*N* [%])	Crude OR (95% CI)	Adjusted* OR (95% CI)
Breastfeeding only				
Male	50/120 (41.7%)	260/593 (43.8%)	1.1 (0.63–1.8)	1.1 (0.64–2.0)
Female	41/121 (33.9%)	268/612 (43.8%)	0.5 (0.29–0.78)	0.5 (0.29–0.79)
Mixed feeding				
Male	45/120 (37.5%)	196/593 (33.1%)	1.3 (0.74–2.1)	1.4 (0.78–2.4)
Female	40/121 (33.1%)	219/612 (35.8%)	0.6 (0.35–0.93)	0.6 (0.34–0.93)
Formula only				
Male	25/120 (20.8%)	137/593 (23.1%)	Reference	Reference
Female	40/121 (33.3%)	125/612 (20.4%)	Reference	Reference

* Adjusted for year of birth, season of birth, presence of siblings, and socioeconomic status.

TABLE 3. Relationship Between Breastfeeding and Potential Confounders Among Control Neonates

	Exclusive Breastfeeding (OR [95% CI])	Mixed Feeding (OR [95% CI])
Male sex	0.89 (0.66–1.2)	0.82 (0.60–1.1)
Birth weight ≥2500 g	3.6 (1.4–9.2)	0.90 (0.44–1.9)
Maternal age <22 y	0.19 (0.09–0.42)	0.73 (0.40–1.3)
Year of birth ≥ 1995	1.8 (1.3–2.4)	1.5 (1.1–2.0)
Birth during winter season (December–March)	1.2 (0.84–1.6)	1.1 (0.81–1.6)
Siblings present	1.1 (0.79–1.4)	0.84 (0.62–1.2)
At-risk family	0.27 (0.18–0.40)	0.74 (0.52–1.1)
White race	2.0 (1.4–2.7)	0.59 (0.43–0.82)

to pathogens circulating within the household and local community and thus would be amenable to influence by infant feeding practice. Our findings that these infections were diagnosed on average during the third week of life and more likely during the winter season and in households with siblings present support the contention that these were primarily community-acquired respiratory tract infections.

Among studies of breastfeeding and respiratory infection, some have found a protective role for breastfeeding,[9–14] whereas others have not.[15–17] However, most have not commented on effect modification by infant sex. Notably, the majority of these studies focused on outcomes during the first 6 months to 1 year of life and not the neonatal period. It may be that, if breastfeeding's protective effect against respiratory infections is modified by sex, then it is an effect confined to either the neonatal or the early infancy period.

This apparent sex specificity of breastfeeding's protective effect against very early respiratory tract disease has been found in 1 other study. Wright et al[11] reported a cohort study of wheezing illness among infants in the first year of life. They found that among non-Mexican American infants, girls had an 11-fold increased risk of wheezing illness during the first 4 months of life if they were breastfed for < month, shared a room, and had a history of parental childhood respiratory difficulty. Among non-Mexican American boy infants, the combination of less breastfeeding and the other 2 covariates was not associated with the risk of disease during the first 4 months of life. Of note, the definition of respiratory tract disease used in by Wright et al differed from ours in requiring wheeze and an abnormal chest radiograph. In addition, their analysis included the first 4 months of life and was not confined to the neonatal period.

We believe that it is unlikely but possible that case detection bias may have contributed to the observed effect modification by infant sex. We relied on clinicians' records to determine the presence or absence of respiratory tract infections. Theoretically, neonatal boys, with lower absolute and relative pulmonary flow rates[18] and airways more susceptible to obstruction may have presented to their pediatricians with more heterogeneous respiratory conditions that were then diagnosed as respiratory tract infections. This heterogeneity might obscure any effect that breastfeeding has on true respiratory tract infections and lead to a null finding among boys. Conversely, neonatal girls may have been more likely to be diagnosed with respiratory infections when they truly had an infectious process whose risk was modifiable by infant feeding practice. However, if this differential case assignment were true, then one would anticipate a higher case detection rate among boys. This was not observed, leading us to believe that it was not an important factor.

We did not ascertain subclinical infections. Although unlikely, if families who breastfed their children were less likely to bring their children's symptoms to the pediatrician's attention, then confounding bias consistent with our results may have been introduced. This, however, would not explain the sex specificity found.

We sought and controlled for the presence of confounding biases known to modulate the association between breastfeeding and infant infection. Our measure of socioeconomic status likely had some misclassification as a result of reliance on census tract level data. We were unable to control for parental smoking or sibling child care attendance and thus cannot rule out these known risks as sources of confounding bias. We were unable to control for family history of allergy, and allergy to formula may manifest with symptoms similar to respiratory infection. However, it seems unlikely that these limitations in our analysis could fully account for the differential association between breastfeeding and respiratory tract infections in neonatal girls versus neonatal boys.

What is the mechanism by which breastfeeding would differentially confer protection against respiratory infections? Clearly, colostrum and breast milk are rich in cellular and acellular factors that could be important to neonatal respiratory immunity.[19] Sex differences in early immunity can be inferred from differential responses to measles vaccine,[20] as well as differential risks of various neonatal infection syndromes (sepsis, meningitis, urinary tract infection, and pustulosis)[21–24] and pathogen-defined childhood infectious diseases (enteroviruses, adenoviruses, and respiratory syncytial virus, among others).[25–27] However, work remains to be done to understand the specific ways in which such differences contribute to neonatal systemic and mucosal immunity in the prevention and amelioration of respiratory disease.

In the absence of a clearly defined immunologic mechanism to support it, this study's main finding, a sex-specific protective association between breastfeeding and risk of neonatal respiratory infection, needs to be interpreted with caution. Nonetheless, whether sex-specific or not, our study supports the contention that the benefits of breastfeeding begin early, within the first 30 days of life.

Currently, exclusive breastfeeding is recommended for approximately the first 6 months of life and breastfeeding with complementary solid foods for at least the first year of life.[28] However, in the United States, most mothers do not breastfeed for this duration.[29] In counseling mothers of newborns about their infant feeding choices, our data suggest that the protective effects of breastfeeding start during the first month of life and that even a short period of exclusive breastfeeding may benefit young children.

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