Gastroenterology 2018;155:696–704

CLINICAL AT

Exposure Concentrations of Infants Breastfed by Women Receiving Biologic Therapies for Inflammatory Bowel Diseases and Effects of Breastfeeding on Infections and Development

Rebecca Matro,[1] Christopher F. Martin,[2] Douglas Wolf,[3] Samir A. Shah,[4] and Uma Mahadevan[5]

[1]Division of Gastroenterology and Hepatology, Oregon Health & Science University, Portland, Oregon; [2]Division of Gastroenterology and Hepatology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; [3]Atlanta Gastroenterology Associates, Atlanta, Georgia; [4]Division of Gastroenterology, Warren Alpert School of Medicine, Brown University, Providence, Rhode Island; and [5]Division of Gastroenterology and Hepatology, University of California San Francisco, San Francisco, California

This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e27. Learning Objective: Upon completion of this CME activity, successful learners will be able to evaluate the risks and benefits of breast feeding while on biologic therapy for inflammatory bowel disease (IBD) and the effects on infant infections and development.

See Covering the Cover synopsis on page 584.

This article has been selected as one of *Gastroenterology*'s "Hot Papers From New Investigators"; original articles from gastroenterologists who are early in their careers and are publishing original content that the Editors have highlighted as high-impact research.

BACKGROUND & AIMS: Exposure to biologic and immunosuppressant agents during breastfeeding is controversial, and there are limited data on safety. We investigated whether biologics are detectable in breast milk from women receiving treatment for inflammatory bowel diseases (IBDs) and whether breastfeeding while receiving treatment is associated with infections or developmental delays. **METHODS:** We performed a multicenter prospective study of women with IBD and their infants, collecting breast milk samples (n = 72) from patients receiving biologic therapy from October 2013 to November 2015. Drug concentrations were measured in all breast milk samples at several time points within 48 hours of collection and within 168 hours for some samples. Child development was assessed using the Ages and Stages Questionnaire 3, completed by 824 women with IBD (treated or untreated) during pregnancy (620 breastfed, and 204 did not). Data on children's health and development were obtained from mothers and pediatricians, along with information on mothers' medication exposure, IBD history, activity, pregnancy, and postpartum complications. We used chi-squared method or Fisher exact test to determine associations between categorical values and compared differences in continuous outcomes between groups using analysis of variance models. The primary outcome was drug concentration of biologic agents in breast milk (from 72 women) at 1, 12, 24, and 48 hours after dosing and also at 72, 96, 120, and 168 hours for available samples. Secondary outcomes were a range of infant infections and Ages and Stages Questionnaire 3–defined developmental delays among all breastfed infants. **RESULTS:** We detected infliximab in breast milk samples from 19 of 29 treated women (maximum, 0.74 μg/mL), adalimumab in 2 of 21 treated women (maximum, 0.71 μg/mL), certolizumab in 3 of 13 treated women (maximum, 0.29 μg/mL), natalizumab in 1 of 2 treated women (maximum, 0.46 μg/mL), and ustekinumab in 4 of 6 treated women (maximum, 1.57 μg/mL); we did not detect golimumab in breast milk from the 1 woman receiving this drug. Rates of infection and developmental milestones at 12 months were similar in breastfed vs non-breastfed infants: any infection, 39% vs 39% in control individuals ($P > .99$) and milestone score, 87 vs 86 in control individuals ($P = .9992$). Rates of infection and developmental milestones did not differ among infants whose mothers received treatment with biologics, immunomodulators, or combination therapy compared with unexposed infants (whose mothers received treatment with mesalamines or steroids or no medication). **CONCLUSIONS:** In a study of women receiving treatment for IBD and their infants, we detected low concentrations of infliximab, adalimumab, certolizumab, natalizumab, and ustekinumab in breast milk samples. We found breastfed infants of mothers on biologics, immunomodulators, or combination therapies to have similar risks of infection and rates of milestone achievement compared with non-breastfed infants or infants unexposed to these drugs. Maternal use of biologic therapy appears compatible with breastfeeding. Clinicaltrials.gov no.: NCT00904878.

Keywords: Breast Milk; Crohn's Disease; Lactation; Ulcerative Colitis.

Abbreviations used in this paper: **ADA, adalimumab; ASQ, Ages and Stages Questionnaire; CD, Crohn's disease; CI, confidence interval; C_{max}, time to maximum serum concentration; CZP, certolizumab pegol; Fc, fragment crystallizable; GOL, golimumab; IBD, inflammatory bowel disease; IBDU, inflammatory bowel disease unclassified; IFX, infliximab; NAT, natalizumab; OR, odds ratio; PIANO, Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes; TNF, tumor necrosis factor; UC, ulcerative colitis; UST, ustekinumab; VED, vedolizumab.**

Most current article

0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2018.05.040

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Biologic medications are commonly used to treat pregnant women with inflammatory bowel disease. Data regarding the safety of breastfeeding while on these medications and transfer of biologics in breast milk is limited.

NEW FINDINGS

Biologic medications are detected in breast milk at very low levels. Breastfed infants of mothers on biologic medications have similar rates of milestone achievement and risk of infection as breastfed infants of mothers not on biologic medications and non-breastfed infants.

LIMITATIONS

Several of the drugs studied had a much smaller sample size. Breast milk samples were only obtained out to 48 hours from drug dosing for most mothers, and to 168 hours for a small group.

IMPACT

This study suggests that biologic medications are compatible with breastfeeding, and there is no increased risk of infection or negative impact on infants exposed to low levels of biologic medications transferred through breast milk.

Available data suggest that the use of biologic (monoclonal antibody) therapy during pregnancy does not lead to an increased rate of adverse pregnancy outcomes in women with inflammatory bowel disease (IBD) or their infants.[1–3] Given the harmful effect of active disease on pregnancy outcomes and the risk of flare with discontinuation of therapy, women are counseled to continue most IBD therapy throughout pregnancy.[4,5] The biologic medications used to treat IBD currently include infliximab (IFX), adalimumab (ADA), certolizumab pegol (CZP), golimumab (GOL), vedolizumab (VED), natalizumab (NAT), and ustekinumab (UST). IFX, ADA, GOL, VED, and UST are IgG1 monoclonal antibodies and can actively cross the placenta and be detectable in the infant at birth.[6–10] CZP does not have a fragment crystallizable (Fc) portion; therefore, placental transfer is passive and minimal.[9]

The American Academy of Pediatrics recommends that women breastfeed for at least 6 months after birth.[11] However, existing data regarding the safety and transfer of biologic agents via breast milk is limited to case reports and small case series.[12–16] The aim of this study was to determine whether biologic agents are detectable in breast milk and to what degree and to assess whether breastfeeding while taking biologic agents affects rate of infections and achievement of developmental milestones of children born to women with IBD.

Materials and Methods

This study is part of the Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) registry, started in 2007. The PIANO registry is a multicenter, national prospective study of pregnancy and neonatal outcomes in women with IBD and their infants among sites of the Crohn's Colitis Foundation Clinical Research Alliance. To date, over 1500 women have been enrolled from 30 sites in the United States. Collection and analysis of breast milk was a predefined secondary endpoint.

Mothers who were enrolled in the PIANO registry completed standard comprehensive questionnaires at intake, during each trimester, at birth, and at months 4, 9, and 12 after birth. Data included maternal demographics, age at IBD diagnosis, disease duration and location, disease activity, specific IBD medications used at conception and in each trimester, and complications during pregnancy and postpartum. History of breastfeeding was obtained when the child was 12 months of age, when mothers were asked whether they had breastfed; the duration of breastfeeding; reasons for never breastfeeding or for stopping; and additional details of IBD medications taken, stopped, or avoided during breastfeeding. The breastfeeding questionnaire was introduced to the cohort beginning in 2010.

For childhood illnesses, mothers and the child's pediatrician provided information about whether the infant was hospitalized, indication for hospitalization, and diagnosis of infection. Serious infections, defined as pneumonia, sepsis, abscess, bladder infection, cellulitis, meningitis, and those requiring hospitalization, were separated from minor infections, including otitis media and upper respiratory tract infections. Outcomes of infants of mothers exposed to a biologic agent were compared with those of infants of mothers exposed to an immunomodulator (azathioprine/6 mercaptopurine), combination therapy (immunomodulator + biologic agent), and unexposed mothers (on mesalamine, steroids, or no medication). Mothers measured and reported infant developmental milestones using the Ages and Stages Questionnaire, third edition (ASQ3), a parent-completed developmental screening tool that assesses communication, gross motor, fine motor, problem-solving, and personal adaptive skills at specific ages from 2–60 months. Normative data have been collected from more than 2000 children from diverse ethnic and socioeconomic backgrounds. Suspected development delay is defined as an ASQ3 score 2 or more standard deviations below national means.[17]

To characterize presence of monoclonal antibodies in breast milk, all actively breastfeeding women enrolled in the PIANO registry from October 2013 to November 2015 who were taking a biologic medication were asked to provide breast milk samples (0.5–2.0 mL/sample). Samples were collected 1, 12, 24, and 48 hours after drug administration, at various time points after birth. In December 2014, the protocol was amended to allow collection of additional samples at 72, 96, 120, and 168 hours after drug dosing.

The study was approved by the institutional review boards at all participating sites, and all women provided written informed consent. The study was funded by a Senior Research Award (Grant ID A127549) from the Crohn's and Colitis Foundation. All authors had access to the study data and reviewed and approved the final manuscript.

Outcome Measures

The primary outcome was the drug concentration and/or detection of the biologic agent in breast milk at 1, 12, 24, and 48 hours after dosing and also at 72, 96, 120, and 168 hours, when available. Secondary outcomes were a range of infant infections and ASQ3-defined developmental delays among all breastfed infants.

Determination of Drug Concentrations in Breast Milk

Drug concentrations in breast milk were measured by a previously described homogenous mobility shift assay for drug concentrations in serum.[18] Briefly, 8 standards were generated by a 1:2 linear dilution using normal human breast milk starting at 10 μg/mL. Three positive controls were generated by spiking 2, 1, and 0.5 μg/mL of drug into normal human breast milk. Twelve microliters of either standard, control, or patient sample were added to individual wells of a 96-well, low-protein–binding, round-bottom plate. Normal human breast milk was added without labeled tumor necrosis factor- α (TNF-α) as background subtraction or with labeled TNF-α as a negative control. Appropriate amounts of labeled TNF-α were added, and final volume was brought up to 300 μL with 1 $\times$ phosphate buffered saline/0.1 $\times$ bovine serum albumin. The samples were then filtered using a 0.2-μm Millipore filter (Billerica, MA), and 100 μL was injected onto the high performance liquid chromatography. The TNF-α/drug complexes and the free TNF-α were then resolved on a Phenomenex (Torrance, CA) Yarra size-exclusion column. A standard curve was generated by plotting the proportion-shifted area [bound TNF-α/(bound TNF-α + unbound TNF-α)] vs drug concentration. Patient samples and controls were then interpolated from this curve to determine the drug concentration. A similar process was used for non-TNF biologics. All samples were analyzed by Prometheus Labs, Inc (San Diego, CA) at no cost.

Statistical Analysis

We examined univariate frequencies and distributional parameters of laboratory test results, outcomes, and characteristics of the study population to identify outliers or implausible values and to permit checking model assumptions. To estimate the associations between maternal IBD drug exposures and developmental milestones and rates of infections, we calculated chi-square or Fisher exact P values for associations between categorical values and estimated F statistics using analysis of variance models to determine differences in continuous outcomes between various exposure groups.

Results

Patient Characteristics

A total of 824 women completed the breastfeeding status questionnaire (Table 1). Overall, 620 (75%) women breastfed, and 204 (25%) did not. The average age of those who breastfed was 31.2 years, and the average duration of disease was 8.4 years. There was no difference in age ($P = .8404$) or duration of disease ($P = .3766$) between those who breastfed and those who did not. Of the women who breastfed, 58% had Crohn's disease (CD), 40% had ulcerative colitis (UC), and 2% had inflammatory bowel disease unclassified (IBDU). Of those who completed the breastfeeding survey, 72 women submitted breast milk samples. Women who provided breast milk samples were of similar age (31.8 years) and had similar disease duration (9.1 years) as women who did not. Women with lower gestational disease activity were more likely to provide breast milk samples, with women in the lowest quartile of disease activity more than 3 times as likely to provide a sample than those in highest quartile ($P = .0361$). Of those women who submitted breast milk samples, 68% had CD, 28.6% had UC, and 3.6% had IBDU.

Table 1. Maternal Characteristics

Characteristics	Overall PIANO n = 824	Breastfed: yes n = 620	Breastfed: no n = 204	Breast milk sample: yes n = 72
Age, *y*, mean (SD)	31.2 (4.6)	31.2 (4.5)	31.3 (4.9)	31.8 (3.2)
Duration of disease, *y*, mean (SD)	8.5 (6.2)	8.4 (6.3)	8.8 (6.0)	9.1 (7.1)
Disease type, n (%)				
UC	316 (38.3)	250 (40.3)	66 (32.4)	8 (28.6)
CD	487 (59.1)	357 (57.6)	130 (63.7)	19 (67.9)
IBDU	21 (2.5)	13 (2.1)	8 (3.9)	1 (3.6)
Medication, n (%)				
Control	244 (29.6)	208 (33.5)	36 (17.6)	0 (0)
Group A	158 (19.2)	102 (16.5)	56 (27.5)	0 (0)
Group B	322 (39.1)	243 (39.2)	79 (38.7)	65 (91.3)
Group AB	100 (12.1)	67 (10.8)	33 (16.2)	7 (9.7)
Biologic, n (%)				
Infliximab	228 (28)	168 (27)	60 (29)	29 (40.3)
Adalimumab	136 (17)	99 (16)	37 (18)	21 (29.2)
Certolizumab	72 (9)	54 (9)	18 (9)	13 (18.6)
Golimumab	1 (0)	1 (0)	0 (0)	1 (1.4)
Natalizumab	12 (1)	8 (1)	4 (2)	2 (2.8)
Ustekinumab	6 (1)	6 (1)	0	6 (8.3)
Disease activity, n (%)				
None	562 (69.5)	441 (72.3)	121 (60.8)	55 (77.5)
Mild	152 (18.8)	105 (17.2)	47 (23.6)	13 (18.3)
Moderate	89 (11.0)	63 (10.3)	26 (13.1)	2 (2.8)
Severe	6 (0.7)	1 (0.2)	5 (2.5)	1 (1.4)

SD, standard deviation.

Table 2. Breastfeeding and Drug Exposure

Group	Breastfed, n (%)		Total, n
	No	Yes	
Unexposed	36 (15)	208 (85)	244
Group A: thiopurine exposure	56 (35)	102 (65)	158
Group B: biologic exposure	79 (25)	243 (75)	322
Group AB: combination therapy exposure	33 (33)	67 (67)	100
Total	204 (25)	620 (75)	824

Among the 824 women with information on breastfeeding, there was no significant difference in breastfeeding status between those with CD, UC, and IBDU. The likelihood of breastfeeding decreased with increasing disease activity (Table 1). Among women who breastfed, women with moderate (10.3%) or severe (0.2%) disease activity were less likely to breastfeed than women with no (72.3%) or mild (17.2%) disease activity ($P = .0018$). Unexposed women (85%) were significantly more likely to breastfeed compared with women on immunomodulators (65%), biologics (75%), and combination therapy (67%) ($P < .0001$) (Table 2). Compared with unexposed women, those receiving biologic monotherapy were half as likely to breast feed (odds ratio [OR], 0.53; 95% confidence interval [CI], 0.34–0.82]), whereas those on immunomodulators or combination therapy were even less likely (immunomodulators alone: OR, 0.32; 95% CI, 0.20–0.51; combination therapy, OR, 0.35; 95% CI, 0.20–0.61). Women receiving biologic monotherapy were significantly more likely to breastfeed than women on combination therapy or immunomodulators (OR, 1.69; 95% CI, 1.12–2.55).

Among women who did not breastfeed, the most common reasons were concerns about exposing their baby to IBD medications (40%, 48/121) and personal preference (24%, 19/121) (Figure 1). Ten percent of patients said their doctor recommended that they not breastfeed. Sixteen of 26 patients who reported "other" for not breastfeeding provided specific reasons, which were primarily related to difficulty with milk production or latching and work schedules. Reasons for not breastfeeding were similar regardless of type of drug exposure. Few women (13%, 80/626) reported stopping an IBD medication during or after pregnancy to breastfeed. In addition, 12% (75/634) of women chose not to take an additional IBD medication to breastfeed. At 1 year, 28% (172/623) of women were still breastfeeding, and 27% (171/623) had stopped because of personal preference or the baby's age. Duration of breastfeeding did not differ among drug exposure groups, but women with higher disease activity breastfed for a shorter duration ($P = .04$).

Breast Milk Concentrations

Seventy-two women submitted breast milk samples: 29 IFX, 21 ADA, 13 CZP, 1 GOL, 6 UST, and 2 NAT (Table 3). Only 10% (7/72) of women were taking concomitant immunomodulators. The date of the last dose of drug before birth was available for 19 women, with a mean of 41.7 (range, 7–98) days.

Infliximab. Among the 29 women receiving IFX, only 1 woman was receiving a concomitant immunomodulator. Nineteen of 29 (66%) women had at least 1 sample with a detectable breast milk infliximab concentration. Maximum breast milk concentration was detected between 24 and 48 hours after infusion (range, 0.15–0.74 μg/mL). Seventeen (59%) women who submitted samples had the drug detected at 48 hours (mean concentration, 0.2 μg/mL). Eight women submitted samples 168 hours after infusion, of whom 5 had detectable concentrations. All those with detectable concentrations at 72 hours or later also had detectable concentrations between 1 and 48 hours after infusion (mean concentration, 0.1 μg/mL).

Adalimumab. Twenty-one women on ADA submitted breast milk samples, and 4 of those were receiving an immunomodulator. ADA was detected in breast milk in only 2 patients (9.5%), 1 receiving an immunomodulator, with

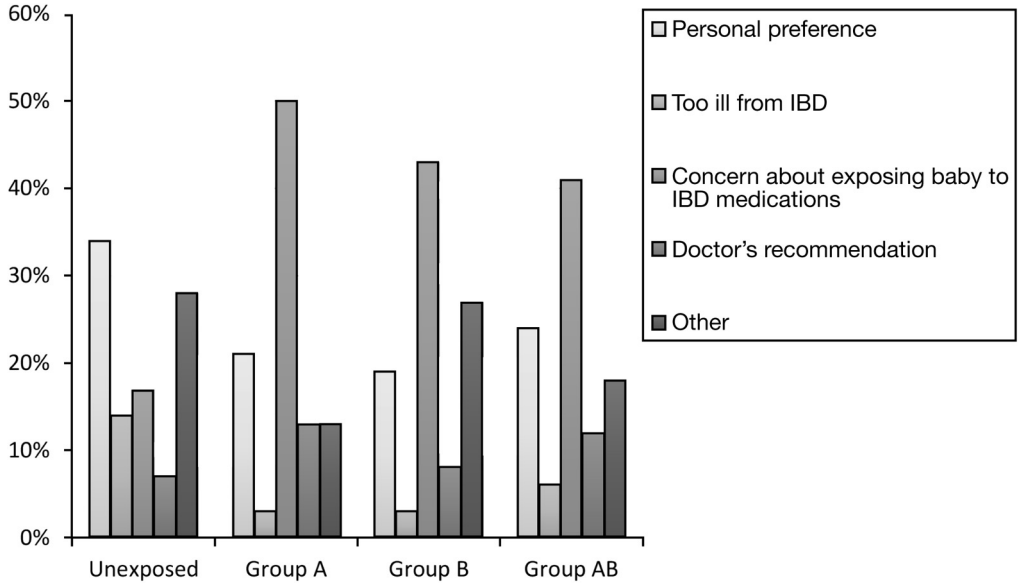

Figure 1. Decision not to breastfeed by drug exposure. Reasons patients did not breastfeed based on drug exposure. Group A, thiopurine exposure only. Group B, biologic exposure only. Group AB, combination therapy exposure.

Table 3. Breast Milk Drug Levels and Data

Drug	Total Patients, n	Total patients with a detectable level, n (%)	Peak (range), *μg/mL*	Peak time range, *hr*
Infliximab	29	19 (66.0)	0.74 (0.15–0.74)	24–48
Adalimumab	21	2 (9.5)	0.71 (0.45–0.71)	12–24
Certolizumab	13	3 (23.0)	0.29 (0.27–0.29)	24–48
Golimumab	1	0 (0)	N/A	N/A
Ustekinumab	6	4 (66.7)	1.57 (0.72–1.57)	12–24
Natalizumab	2	1 (50.0)	0.46	24

N/A, not applicable.

the maximum concentration seen between 12 and 24 hours after injection (range, 0.45–0.71 μg/mL). Seven women provided breast milk samples out to 7 days, and ADA was undetectable at all time points in those women.

Certolizumab pegol. Thirteen women receiving CZP submitted breast milk samples, and 2 of them were also on an immunomodulator. The drug was detected in 3 women (23%) receiving CZP alone, with peak concentrations seen between 12 and 48 hours (range, 0.27–0.29 μg/mL). Two women with undetectable concentrations in the first 48 hours after injection submitted breast milk samples out to 7 days, and CZP was undetectable at all time points.

Golimumab. One woman on GOL submitted breast milk samples up to 7 days after her injection. The drug was not detected in any of the samples.

Ustekinumab. Six women receiving UST provided samples. None were taking a concomitant immunomodulator. UST was detected in 4 of 6 (67%) samples, with peak concentrations seen between 12 and 72 hours after injection (range, 0.72–1.57 μg/mL). All of the mothers with detectable concentrations submitted samples out to 7 days, and 3 of those had concentrations detected beyond 48 hours.

Natalizumab. Two women receiving NAT submitted breast milk samples out to 48 hours. The drug was detected in breast milk in 1 woman at 12 hours and 24 hours (0.26 and 0.46 μg/mL, respectively).

Infection, Growth, and Development

Among the 824 women with breastfeeding data, per the ASQ3, there was no increased risk of developmental delay or lack of milestone achievement at 12 months in infants who were breastfed compared with not breastfed (Table 4), and ASQ3 scores of breastfed infants did not differ by maternal medical therapy (Table 5). There was no difference in rates

Table 4. Effect of Breastfeeding on Growth, Developmental Milestones, and Infection

Outcome (infant age)	Overall PIANO n = 824	Breastfed: yes n = 620	Breastfed: no n = 204	*P* value
NICU stay (0–12 mo), n (%)				
No	728 (88)	552 (89)	176 (86)	.3141
Yes	96 (12)	68 (11)	28 (14)	
Milestone scores (12 mo), mean (SD)	87 (10)	87 (9.7)	86 (11)	.9992
Infection, any (4 mo), n (%)				
No	705 (86)	533 (86)	172 (84)	.4869
Yes	116 (14)	84 (14)	32 (16)	
Infection, any (9 mo), n (%)				
No	512 (68)	384 (68)	128 (69)	.8555
Yes	236 (32)	179 (32)	57 (31)	
Infection, any (12 mo), n (%)				
No	500 (61)	376 (61)	124 (61)	>.99
Yes	324 (39)	244 (39)	80 (39)	
Infection, no OM, (4 mo), n (%)				
No	755 (92)	569 (92)	186 (91)	.6564
Yes	66 (8)	48 (8)	18 (9)	
Infection, no OM, (9 mo), n (%)				
No	643 (86)	487 (87)	156 (84)	.4654
Yes	105 (14)	76 (13)	29 (16)	
Infection, no OM, (12 mo), n (%)				
No	659 (80)	495 (80)	164 (80)	.9198
Yes	165 (20)	125 (20)	40 (20)	

NICU, neonatal intensive care unit; OM, otitis media; SD, standard deviation.

Table 5. Effect of Drug Exposure on Infant Growth, Development, and Infection Among Breastfed Infants

Outcome (infant age)	Overall n = 620	Unexposed n = 208	Group A n = 102	Group B n = 243	Group AB n = 67	*P* value
Duration breastfed, mean (SD)	7.4 (4.2)	7.2 (4.2)	7.3 (4.1)	7.4 (4.2)	7.2 (4.4)	.9788
Milestone scores (12 mo), mean (SD)	87 (10)	87 (11)	87 (9)	88 (9)	88 (9)	.5491
NICU stay, (12 mo), n (%)						
No	552 (89)	191 (92)	93 (91)	212 (8)	56 (84)	.3141
Yes	68 (11)	17 (8)	9 (9)	31 (13)	11 (16)	
Infection, any (4 mo), n (%)						
No	533 (86)	182 (88)	93 (92)	201 (83)	57 (87)	.4869
Yes	84 (14)	26 (13)	8 (8)	41 (17)	9 (14)	
Infection, any (9 mo), n (%)						
No	384 (68)	126 (68)	64 (70)	153 (67)	41 (68)	.8555
Yes	179 (32)	58 (32)	28 (30)	74 (33)	19 (32)	
Infection, any (12 mo), n (%)						
No	376 (61)	114 (55)	68 (67)	153 (63)	41 (61)	>.99
Yes	244 (39)	94 (45)	34 (33)	90 (37)	26 (39)	
Infection, no OM (4 mo), n (%)						
No	569 (92)	193 (93)	98 (97)	215 (89)	63 (95)	.6564
Yes	48 (8)	15 (7)	3 (3)	27 (11)	3 (5)	
Infection, no OM (9 mo), n (%)						
No	487 (87)	163 (89)	84 (91)	188 (83)	52 (87)	.4654
Yes	76 (13)	21 (11)	8 (9)	39 (17)	8 (13)	
Infection, no OM (12 mo), n (%)						
No	495 (80)	160 (77)	86 (84)	197 (81)	52 (78)	.9198
Yes	125 (20)	48 (23)	16 (16)	46 (19)	15 (22)	

NICU, neonatal intensive care unit; OM, otitis media; SD, standard deviation.

of infection among infants who were breastfed and those who were not (Table 4). Breastfed infants exposed to immunomodulators, biologics, or combination therapy had similar milestone achievement and were also not more likely to have an infection in the first 12 months of life compared with unexposed infants or infants who were not breastfed (Table 5). This was true for all infections and also when excluding otitis media, the most common infection. Of note, breastfed infants were numerically more likely (39% vs 36%) to attend daycare and/or have a sibling in daycare (62% vs 48%).

Discussion

To our knowledge, this is the largest prospective observational study evaluating biologic breast milk transfer from women with IBD to their infants and includes data for nearly all of the biologic medications currently used to treat IBD. In this study, IFX, ADA, CZP, UST, and NAT were all detected in breast milk samples, but at very low concentrations. Concomitant immunomodulator use did not affect drug detection in breast milk. Among the cohort of 824 infants, breastfeeding while receiving biologic therapy did not adversely affect the rate of infection or achievement of developmental milestones compared with not breastfeeding.

Recommendations have historically been for women receiving anti–TNF-α or biologic therapy to avoid breastfeeding. However, breastfeeding should be low risk, because IgA is the predominant immunoglobulin found in breast milk, and the biologic agents evaluated here are all in the IgG subclass.[19,20] Therefore, secretion and transfer in breast milk should be minimal.

Current data evaluating the concentrations of the anti–TNF-α drugs IFX, ADA, and CZP in breast milk are limited to case reports.[8,9,12–16] These have shown trivial transfer of IFX,[13–16] ADA,[12,14] CZP,[21] and UST,[22] similar to our study.

Monoclonal antibody therapy may be absorbed to some small degree from the gut. An infant who had no intrauterine infliximab exposure and was exposed to the drug only through breast milk after the mother initiated IFX in the postpartum period had a serum concentration of 1.7 μg/mL 5 days after the mother's second IFX infusion.[14] The mechanism of absorption is not clear, but it has been postulated to involve the FcRn, which is expressed in a variety of neonatal tissues and the intestinal cells of adults and fetuses.[23,24]

We considered whether it would be helpful to understand the serum pharmacokinetics of these biologic medications to predict degree and timing of detectable breast milk concentrations by looking at the drug half-life and C_{max} (time to maximum serum concentration). Half-life and C_{max} for each agent are listed in Table 6.[22,25–29]

For IFX, 8 women submitted samples our to 168 hours, of whom 5 had detectable concentrations beyond 48 hours as well as between 1 and 48 hours after infusion. Therefore, it is unlikely that we missed any samples with detectable IFX concentrations beyond 48 hours among the women who did not have detectable concentrations between 1 and 48 hours and extended data. For ADA, it is possible that the

Table 6. Biologic Pharmacokinetics and Peak Breast Milk Level

Drug	Half-life	C_{max}	Time of peak BM level in study
Infliximab[25]	8–9.5 d	Immediately after infusion	24–48 hr
Adalimumab[26]	14 d	5–131 h	12–24 hr
Certolizumab[27]	14 d	56–171 h	12–48 hr
Golimumab[28]	14 d	48–144 h	N/A
Ustekinumab[22]	15–45 d	168–312 hours	12–72 hr
Natalizumab[29]	11 d	Immediately after infusion	24 hr

BM, breast milk; N/A, not applicable.

drug would be detected with sampling out to 7 days when peak serum concentration occurs. However, in our small sample, peak breast milk concentration was seen 12–24 hours after dosing, and no drug was detected in 7 women who provided samples out to 168 hours. Similarly, 2 women receiving CZP who provided samples out to 168 hours did not have detectable breast milk concentrations at any time point. In our small sample size for UST, peak breast milk concentrations were seen 12–72 hours after injection, and the drug was detected beyond 48 hours in 75%. Finally, for NAT, neither of the 2 women in our study submitted samples beyond 48 hours. However, as was the case in a prior case report, the drug could be detected with extended sampling.[30]

Finally, the overall rate of breastfeeding in the PIANO registry was 75%, which is slightly lower than the average rate of 81.1% of infants who start to breastfeed in the United States.[31] Our study shows that significantly fewer women taking immunomodulators and biologics breastfeed compared with women not taking these medications. The most common reasons for not breastfeeding were concern for drug transfer to the infant and personal preference. Physician recommendation was also influential. Better data and provider and patient education should help increase rates of breastfeeding in this population.

This study has several strengths and limitations. It is the largest long-term, prospective observational study of nursing mothers and their infants. Breast milk concentrations were measured at multiple time points and infants were followed up to at least 1 year. In addition, breast milk concentrations were analyzed using assays that calibrated the standard curve with breast milk. All drug concentrations were analyzed with this assay methodology. One limitation is that the sample sizes were small for GOL, NAT, and UST. Next, lack of extended breast milk samples collected may be important. Only 22 of 72 (14%) women submitted breast milk samples between 48 hours and 168 hours after drug dosing. Whereas infusion-based medications have a C_{max} immediately after infusion, injection-based drugs have a longer time to C_{max}. Although this was not seen in our small sample of injection-based drugs, it is possible that the drugs could be detected with extended sampling. Next, breastfeeding in general has been associated with lower rates of infection, including otitis media.[32,33] We looked at all infections, including otitis media, and infections excluding otitis media to be able to capture more serious infections. We also queried mothers regarding daycare exposure. Although our sample size with breast milk samples is small, the overall cohort of 824 women with breastfeeding data is well characterized and supports the low risk associated with breastfeeding while receiving biologic therapy.

Finally, infant cord drug concentrations at birth and serum concentrations after birth as a result of placental transfer may have a greater impact on infection and development outcomes than breast milk transfer, and time of breast milk sample after birth may also be important. In this study, breast milk samples were mostly obtained within 3 months of birth, when some concentration of placental transfer would be present. We did not have serum samples from all infants who also had breast milk concentrations, so we were unable to perform this analysis. However, among 14 infants who did have serum concentrations at birth, there was no correlation between infant serum concentration, age at breast milk sample, or days between blood and breast milk sample. There was also no correlation between age at breast milk sample and detection in breast milk. Furthermore, prior studies have shown no difference in infection outcomes in infants exposed in utero to biologic monotherapy based on concentration of the drug in infants at birth.[34,35] Therefore, although lack of placental transfer data is a limitation of our study, it is not likely to have an impact on infection outcomes.

In conclusion, lactation is compatible with the use of maternal biologic therapy based on minimal transfer rates in breast milk and no association with infant infections and achievement of developmental milestones. Continued long-term prospective data collection is necessary, and more data are needed to characterize the pharmacokinetics of the newer biologic agents GOL, UST, and VED.

References

1. Mahadevan U, Martin CF, Sandler RS, et al. PIANO: a 1000 patient prospective registry of pregnancy outcomes in women with IBD exposed to immunomodulators and biologic yherapy [abstract]. Gastroenterology 2012; 142:S-149.
2. Mahadevan U, Martin C, Chambers C, et al. Achievement of developmental milestones among offspring of women

with inflammatory bowel disease: the PIANO registry [abstract]. Gastroenterology 2014;146:S-1.
3. Schnitzler F, Fidder H, Ferrante M, et al. Outcome of pregnancy in women with inflammatory bowel disease treated with antitumor necrosis factor therapy. Inflamm Bowel Dis 2011;17:1846–1854.
4. Norgard B, Hundborg HH, Jacobsen BA, et al. Disease activity in pregnant women with Crohn's disease and birth outcomes: a regional Danish cohort study. Am J Gastroenterol 2007;102:1947–1954.
5. Nguyen GC, Seow CH, Maxwell C, et al. The Toronto consensus statement for the management of inflammatory bowel disease in pregnancy. Gastroenterology 2016; 150:734–757.
6. Gisbert JP, Chaparro M. Safety of anti-TNF agents during pregnancy and breastfeeding in women with inflammatory bowel disease. Am J Gastroenterol 2013; 108:1426–1438.
7. Horst S, Kane S. The use of biologic agents in pregnancy and breastfeeding. Gastroenterol Clin North Am 2014; 43:495–508.
8. Zelinkova Z, de Haar C, de Ridder L, et al. High intrauterine exposure to infliximab following maternal anti-TNF treatment during pregnancy. Aliment Pharmacol Ther 2011;33:1053–1058.
9. Mahadevan U, Wolf DC, Dubinsky M, et al. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2013;11:286–292.
10. Haghikia A, Langer-Gould A, Rellensmann G, et al. Natalizumab use during the third trimester of pregnancy. JAMA Neurol 2014;71:891–895.
11. American Academy of Pediatrics. Breastfeeding and the use of human milk. Pediatrics 2012;129: e827–e841.
12. Ben-Horin S, Yavzori M, Katz L, et al. Adalimumab level in breast milk of a nursing mother [letter to the editor]. Clin Gastroenterol Hepatol 2010;8:475–476.
13. Ben-Horin S, Yavzori M, Kopylov U, et al. Detection of infliximab in breast milk of nursing mothers with inflammatory bowel disease. J Crohns Colitis 2011; 5:555–558.
14. Fritzsche J, Pilch A, Mury D. IFX and ADA use during breast feeding. J Clin Gastro 2012;46:718–719.
15. Stengel J. Is IFX safe to use while breastfeeding? World J Gastro 2008;14:3085–3087.
16. Kane S, Ford J, Cohen R. Absence of IFX in infants and breast milk from nursing mothers receiving therapy for CD before and after delivery. J Clin Gastro 2009;43:613–616.
17. Squires J, Twombly E, Bricker D, et al. ASQ-3™ user's guide. 3rd ed. Baltimore: Brookes Publishing Co, 2009.
18. Wang SL, Ohrmund L, Hauenstein S, et al. Development and validation of a homogeneous mobility shift assay for the measurement of infliximab and antibodies-to-infliximab levels in patient serum. J Immunol Methods 2012;31;382(1–2):177–188.
19. Van de Perre P. Transfer of antibody via mother's milk. Vaccine 2003;21:3374–3376.
20. Gasparoni A, Avanzini A, Ravagni Probizer F, et al. IgG subclasses compared in maternal and cord serum and breast milk. Arch Dis Child 1992;67:41–43.
21. Clowse MEB, Forger F, Hwang C, et al. Evaluating transfer of certolizumab pegol into breast milk: results from a prospecting, postmarketing, multicenter pharmacokinetic study. J Am Acad Dermatol 2017;76:AB127.
22. Stelara [package insert]. Horsham, PA: Janssen Pharmaceutical Companies, 2016. https://www.stelarainfo.com/pdf/prescribinginformation.pdf. Accessed April 4, 2017.
23. Israel EJ, Taylor S, Wu Z, et al. Expression of the neonatal Fc receptor FcRn, on human intestinal epithelial cells. Immunology 1997;92:69–74.
24. Shah U, Dickinson BL, Blumberg RS, et al. Distribution of the IgG Fc receptor, FcRn, in the human fetal intestine. Pediatr Res 2003;53:295–301.
25. Infliximab [package insert]. Horsham, PA: Janssen Pharmaceutical Companies, 2015. http://www.remicadehcp.com/shared/product/remicade/prescribing-information.pdf. Accessed April 21, 2017.
26. Adalimumab [package insert]. North Chicago, IL: AbbVie Inc, 2017. http://www.rxabbvie.com/pdf/humira.pdf. Accessed April 21, 2017.
27. Certolizumab [package insert]. Smyma, GA: UCB, Inc, 2016. https://www.cimzia.com/assets/pdf/Prescribing_Information.pdf. Accessed April 21, 2017.
28. Golimumab [package insert]. Horsham, PA: Janssen Pharmaceutical Companies, 2017. https://www.simponihcp.com/sites/www.simponihcp.com/files/prescribing-information.pdf. Accessed April 21, 2017.
29. Natalizumab [package insert]. Cambridge, MA: Biogen, Inc, 2015. https://www.tysabrihcp.com/content/dam/commercial/multiple-sclerosis/tysabri/hcp/en_us/pdf/PI%20I61061-22_clean.pdf. Accessed April 21, 2017.
30. Baker T, Cooper S, Kessler L, et al. Transfer of natalizumab into breast milk in a mother with multiple sclerosis. J Human Lact 2015;31:233–236.
31. Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Division of Nutrition, Physical Activity, and Obesity. Breastfeeding report card: progressing toward national breastfeeding goals 2016. https://www.cdc.gov/breastfeeding/data/reportcard.htm. Accessed April 12, 2017.
32. Sabirov A, Casey J, Murphy T, et al. Breastfeeding is associated with a reduced frequency of acute otitis media and high serum antibody levels against NTHi and outer membrane protein vaccine antigen candidate P6. Pediatr Res 2009;66:565–570.
33. Li R, Dee D, Li CM, et al. Breastfeeding and risk of infections at 6 years. Pediatrics 2014;134: S13–S20.
34. Mahadevan U, Martin C, Kane S, et al. Do infant serum levels of biologic agents at birth predict risk of adverse outcomes? Results from the PIANO Registry. Gastroenterology 2016;150:S91–S92.
35. Julsgaard M, Christensen LA, Gibson PR, et al. Concentrations of adalimumab and infliximab in mothers and

newborns, and effects on infection. Gastroenterology 2016;151:110–119.

Received January 29, 2018. Accepted May 22, 2018.

Reprint requests
Address requests for reprints to: Rebecca Matro, MD, Oregon Health & Sciences University, 3181 SW Sam Jackson Park Road, L461, Portland, Oregon 97239-3098. e-mail: matro@ohsu.edu; fax: (503) 494-8776.

Acknowledgments
Author contributions: Rebecca Matro: acquisition of data, analysis and interpretation of data, drafting of manuscript, and critical revision of manuscript for important intellectual content; Christopher Martin: acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and statistical analysis; Douglas Wolf: critical revision of the manuscript for important intellectual content; Samir A. Shah: critical revision of the manuscript for important intellectual content; Uma Mahadevan: study concept and design, acquisition of data, analysis and interpretation of data, drafting of manuscript, critical revision of manuscript for important intellectual content, obtained funding, study supervision.

Conflicts of interest
Douglas Wolf is a consultant for AbbVie, Janssen, Takeda, and UCB. Samir A. Shah participates in the speakers bureau for AbbVie, Janssen, and Takeda. Uma Mahadevan is a consultant for AbbVie, Janssen, and Takeda. The remaining authors disclose no conflicts.

Funding
Funding was provided by a senior research award (Grant ID A127549) from the Crohn's and Colitis Foundation (to Uma Mahadevan). Prometheus Laboratories provided breast milk sample testing at no cost. They did not have any role in the study design, collection, analysis, or interpretation of data.