

The Role of Breastfeeding in Postpartum Disease Activity in Women with Inflammatory Bowel Disease

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- BACKGROUND:** Women with inflammatory bowel disease (IBD) have an increased risk of experiencing a flare in the postpartum period. Work in other autoimmune disorders has found that breastfeeding may be associated with an increased risk for developing postpartum disease relapse.
- AIM:** To assess the association between breastfeeding behavior and postpartum disease activity.
- METHODS:** Women with IBD followed at a tertiary care center with a history of childbirth within the past 5 yr were recruited. Medical records were reviewed for disease type, disease activity during and after pregnancy, medication use, smoking, and breastfeeding behavior. The exposure of interest was breastfeeding prior to the onset of disease activity following a successful asymptomatic pregnancy.
- RESULTS:** One hundred and twenty-two consecutive women who fit eligibility criteria were studied. Overall, only 44% (54/122) of the women had breastfed their infant. Reasons included physician recommendation, fear of medication interactions, and personal choice. Forty-three percent (23/54) of those who breastfed experienced a postpartum flare of their disease. The unadjusted odds ratio for disease activity with a history of breastfeeding was 2.2 (95% CI 1.2–3.9, $p = 0.004$). When stratified by disease type, the OR for ulcerative colitis was 0.89 (0.29–2.7, $p > 0.05$) and Crohn's disease 3.8 (1.9–7.4, $p < 0.05$). When adjusted for medication cessation, the OR became nonsignificant.
- CONCLUSIONS:** A significant number of women with IBD do not breastfeed their children. Any relationship between breastfeeding and disease activity may be more a consequence of discontinuation of IBD therapies.

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BACKGROUND

Inflammatory bowel disease (IBD) constitutes several chronic inflammatory conditions affecting the gastrointestinal tract. It is thought to be an autoimmune process, with a course that is characterized by episodes of disease activity followed by prolonged periods of quiescence. Women who are pregnant have been found to have variable courses—the level of disease activity is most closely associated with the level of activity at the time of conception (1, 2). If a woman has quiescent disease at the time of conception, she is no more likely to experience a flare than a non-pregnant woman. If a woman has active symptoms at the time of conception, she has approximately equal chances of having worsening disease, continued symptoms, or disease improvement. There also appears to be a risk for flaring in the postpartum period, and it is unclear at this time what factors may increase this risk although certain hypotheses exist. Discontinuation of medications and resumption of smoking are behaviors that are independently associated with increased disease activity. The significant change in the hormonal milieu following delivery has also been proposed.

The advantages and benefits of breastfeeding for the neonate are well established, including the decreased risk of developing IBD (3, 4). Work in the area of other autoimmune diseases, however, suggests an adverse effect of nursing on disease activity in the mother (5–7). *In vitro* studies suggest that prolactin possesses certain proinflammatory properties, including upregulation of tumor necrosis factor (8). The role of breastfeeding in disease activity and recurrence in IBD has not been previously investigated. The aim of this study was to examine the potential association between breastfeeding and disease activity in those women with either ulcerative colitis (UC) or Crohn's disease (CD).

METHODS

Patients

Women receiving regular care at the University of Chicago Inflammatory Bowel Disease Center were eligible. Those women between 21 and 50 presenting for a routine clinic visit were queried for a history of childbirth within the previous 5 yr and an asymptomatic pregnancy; those with a positive response were recruited. Upon signing informed

consent, subjects completed a one-page questionnaire during the scheduled clinic visit.

Data

Information collected on the questionnaire included diagnosis, disease activity during and after pregnancy, medication use, tobacco exposure, and breastfeeding. Medical records of each patient were then reviewed for further clinical data regarding disease activity during and after the pregnancy. A postpartum flare was defined as an increase in disease activity within 8 months of delivery.

Data Analysis

Subjects were stratified by diagnosis. The outcome of interest was clinical recurrence of disease, as documented in the chart by an increase in symptoms, a change in medications, or hospitalization. The exposure of interest was a positive history of breastfeeding for at least 4 wk following delivery. Crude odds ratios (OR) along with 95% confidence intervals (CI) and logistic regression analysis to adjust for confounding were performed to estimate the association of breastfeeding on disease activity. A *p*-value of 0.05 was considered statistically significant. All analysis was done using Stata (College Station, TX).

The study was approved by the University of Chicago Institutional Review Board before any patients were recruited.

RESULTS

A total of 122 women were recruited. Forty had UC and eighty-two had CD. Clinical characteristics are shown in Table 1. Overall, only 54 (44%) women had breastfed their infant. The majority of these women had UC, only 29% of the women with CD breastfed her infant. The primary reason indicated by women for not breastfeeding included fear of medication interactions (52%), physician recommendation (30%), and personal choice (18%). Of those women who breastfed, the median duration was 8 months, with a range of 3 to 14 months.

The choice for women with UC to nurse or not did not appear to be associated with disease duration, the number of flares in the 2 yr prior to pregnancy, nor the time since last steroid use; there were no significant differences in these disease characteristics between those who did and did not nurse. In the women with CD, disease duration was not different. However, disease extent was different as was the time since last disease activity. In those women whose disease involved

either jejunum or colon along with the ileum, or had experienced a flare of disease within the past 18 months they were less likely to breastfeed than those with disease limited to the ileum or a longer period of quiescent disease (Table 2).

There were fewer women with CD on immunomodulators as a group, but more had a history of prednisone use during their pregnancy than women with UC (Table 3). More women with CD expressed a desire to stay on medications following delivery for fear of a disease flare, thus deciding not to nurse. The cesarean section rate was not different between the two groups, therefore making this a less likely reason for the observed difference in nursing rates.

Thirty-six (30%) of the total population experienced a postpartum flare. Twenty-three of those 36 (64%) had a history of breastfeeding for at least 1 month prior to the onset of their flare. The overall range of length of time breastfeeding prior to a flare was 4 to 12 wk. The unadjusted OR for the risk of disease activity with a history of breastfeeding was 2.2 (95% CI 1.2–3.9, Table 4). When stratified by disease type, the OR for UC was 0.89 (0.29–2.7) and for CD was 3.8 (1.9–7.4).

The majority of women who breastfed (40/54, 74%) stopped taking their medications prior to breastfeeding. The time of medication cessation was 4 wk prior to the date of anticipated delivery. The majority had discussed the decision to stop medications with their obstetrician or pediatrician, not their gastroenterologist.

When adjusted for medication cessation, the overall OR for breastfeeding decreased to 1.3 (0.8–2.7), 0.9 (0.34–2.5) for UC and 2.1 (1.1–8.5) for CD. Adjustment for disease duration or duration of nursing prior to disease activity did not change the OR.

DISCUSSION

It was of interest to us to find that of the total population, over half of women with IBD in our series did not breastfeed their infants. The majority of these, however, were women with CD. The national rate for breastfeeding is approximately 60%, with active initiations by the U.S. government to increase this number (9). The proportion of women with UC who breastfed was actually higher than the national average while that in the CD patients was significantly lower (29%). The reason cited by most women for not breastfeeding was fear of medication interactions, but it is unclear if this is the entire explanation for such a low percentage of breastfeeders among our CD patients. The medications most often discontinued were mesalamine and the antimetabolites

Table 1. Patient Characteristics

	Age at Index Conception Median (Range)	Years of Disease at Conception Median (Range)	Percentage of Breastfed (n)	Percentage of Flared Postpartum (n)	Smokers During Pregnancy (n)
UC (n = 40)	28 (19–40)	4 (0–12)	75 (30)	28 (11)	0 (0)
CD (n = 82)	27 (20–38)	6 (2–15)	29 (24)	31 (25)	0 (0)

Table 2. Disease Characteristics Based on Breastfeeding Behavior in Crohn's Patients

	Breastfeeding	No Breastfeeding	p-Value
Disease > 5 yr	46	36	> 0.05
Last flare > 2 yr prior to pregnancy	72	10	< 0.03
Disease limited to ileum	67	15	0.04

6-mercaptopurine and azathioprine. No patients were on infliximab during their pregnancy in this series. Most women discussed the decision to stop medications with their obstetrician and/or pediatrician.

Diarrhea in a nursing infant, apparently as a result of the rectal administration of mesalamine, has been reported (10). The mother had ulcerative proctitis and 6 wk after child-birth treatment was initiated for disease activity with 500 mg suppositories twice daily. Her infant developed watery diarrhea an hour after the first dose. Four additional challenges of breastfeeding following suppository administration produced the same results. Plasma and milk concentrations were not obtained at that time. Based on this single report, the American Academy of Pediatrics classified mesalamine as a drug that has produced adverse effects in a nursing infant and should be used with caution during breastfeeding.

In a subsequent study, low concentrations of mesalamine and its metabolite were found in the breastmilk of a woman taking 1 g three times a day orally (11). Maternal serum levels determined at 7 and 11 days postpartum were 0.6 and 1.1 µg/mL, representing milk:plasma ratios for mesalamine of 0.17 and 0.09, and for the metabolite of 16.5 and 6.8. The estimated daily intake by the infant of mesalamine and metabolites was 0.065 mg (0.015 mg/kg) and 10 mg (2.3 mg/kg), respectively, considered to be negligible amounts.

To date there are very little data available regarding antimetabolite milk:plasma ratios. A single case report documents negligible amounts of 6-mercaptopurine in a single sample from a woman taking 6-mercaptopurine after renal transplantation, tested using high performance liquid chromatography (12). Milk analysis studies are currently underway in mothers taking antimetabolites or receiving infliximab during pregnancy.

The effect of breastfeeding on another autoimmune disease has been studied in an animal model. Arthritic mice nursing their pups had worse disease than those mice whose pups were taken away and weaned by normal mice (13). In two human observational studies, women with rheumatoid arthritis had an apparent increased risk for disease activity with breast-

Table 3. Medication History by Disease

	5-ASA (%)	AZA/6MP (%)	Prednisone (%)
UC	30 (75)	5 (12)	5 (12)
CD	38 (46)	7 (8)	20 (24)

Table 4. Odds Ratios for Postpartum Disease Based on Breastfeeding Behavior

	Odds Ratio	95% Confidence Interval
Unadjusted		
Nonbreastfeeder	1.0	
Total population	2.2	1.2–3.9
Ulcerative colitis	0.89	0.29–2.7
Crohn's disease	3.8	1.9–7.4
Adjusted for medication cessation		
Total population	1.3	0.8–2.7
Ulcerative colitis	0.9	0.34–2.5
Crohn's disease	2.1	1.1–8.5

feeding (14, 15). In the study by Barrett *et al.*(14), disease activity was compared in nonbreastfeeders to first time and repeat breastfeeders. First time breastfeeders had increased disease activity 6 months postpartum based on subjective and objective criteria, after adjusting for medication use. Forty-six percent of women with severe rheumatoid arthritis *versus* only 26% of those with mild disease had breastfed longer than 6 months before disease onset. Having more than three breast-fed children increased risk of poor disease prognosis by nearly fourfold (OR 3.7). In the study by Hampl and Papa (15), breastfeeding was associated with an increased risk developing the rheumatoid arthritis, particularly after the first pregnancy.

It has been suggested that the biological mechanism for this association is a result of the increased circulating prolactin levels during lactation. Prolactin upregulates tumor necrosis factor production and is also produced by activated immunocytes (16). This has been postulated for women who have not only rheumatoid arthritis, but also multiple sclerosis. The increased levels of tumor necrosis factor, thought to play a central role in CD, may explain why there is a significant difference in CD and not UC.

We did not find an increased risk of disease activity with breastfeeding. However, there are several limitations to our study. First, this was a relatively small sample size for the number of women with a history of breastfeeding, especially in CD patients. With fewer than 50% of women breastfeeding, we could be underestimating the risk due to a lack of power. While the most rigorous methodology to assess risk would be a randomized trial, it would be unethical in this clinical scenario. A prospective cohort study with more subjects would take an unreasonable amount of time since pregnancy is a relatively rare event. This is the first study to look at inflammatory bowel disease and does represent a larger number of subjects than in the other studies in the rheumatology literature.

Secondly, this was a retrospective study, but we corroborated patient surveys with medical records to minimize recall bias. We chose a cut-off of 5 yr to also minimize patient recall bias and to assure availability of adequate medical records.

In conclusion, while we found an increased risk for postpartum disease activity in women who had a history of

breastfeeding, this effect disappeared when adjusted for medication cessation for the entire population. A slightly increased odds was still present in women with CD after adjustment for cessation of medications. A true association between breastfeeding and disease activity may be more a consequence of discontinuation of medications to control disease activity, and thus an important reason why further study into drug metabolism and breastmilk is warranted.

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REFERENCES

1. Miller JP. Inflammatory bowel disease in pregnancy: A Review. *J R Soc Med* 1986;79(4):221–5.
2. Mogadam M, Korelitz BI, Ahmed SW, et al. The course of inflammatory bowel disease during pregnancy and postpartum. *Am J Gastroenterol* 1985;75(4):265–9.
3. Bergstrand O, Hellers G. Breastfeeding during infancy in patients who later develop Crohn's disease. *Scand J Gastroenterol* 1983;18(7):903–6.
4. Whorwell PJ, Holdstak G, Whorwell GM, et al. Bottle feeding, early gastroenteritis, and inflammatory bowel disease. *Br J Me* 1979;1(6160):382–4.
5. Draca S, Levic Z. The possible role of prolactin in the immunopathogenesis of multiple sclerosis. *Med Hypotheses* 1996;47(2):89–92.
6. Jorgensen C, Picot MC, Bologna C, et al. Oral contraception, parity, breastfeeding and severity of rheumatoid arthritis. *Ann Rheum Dis* 1996;55(2):94–8.
7. Chikanza IC, Petrou P, Chrousos G, et al. Excessive and dysregulated secretion of prolactin in rheumatoid arthritis: Immunopathogenic and therapeutic implications. *Br J Rheumatol* 1993;32(6):445–8.
8. Berczi I. The role of the growth and lactogenic hormone family in immune function. *Neuroimmunomodulation* 1994;1(4):201–16.
9. Ryan AS. The research on breastfeeding in the United States. *Pediatrics* 1997;99(4):1–12.
10. Neils GF. Diarrhoea due to 6-aminosalicylic acid in breast milk. *Lancet* 1989;1:383.
11. Klotz U, Harings-Kaim A. Negligible excretion of 5-aminosalicylic acid in breast milk. *Lancet* 1993;342(8871):618–9.
12. Fagerholm MI, Coulam CB, Moyer TP. Breastfeeding after renal transplantation: 6-mercaptopurine content in human breast milk. *Surg Forum* 1980;3:447–9.
13. Ratkay LG, Weinberg J, Waterfield JD. The effect of lactation in the postpartum arthritis of MRL-lpr/fas mice. *Rheumatology* 2000;39(6):646–51.
14. Barrett JH, Brennan P, Fiddler M, et al. Breastfeeding and postpartum relapse in women with rheumatoid and inflammatory arthritis. *Arthritis Rheum* 2000;43(5):1010–5.
15. Hampl JS, Papa DJ. Breastfeeding related onset, flare and relapse of rheumatoid arthritis. *Nutr Rev* 2001;59(8 Pt 1):264–8.
16. Meli R, Gualillo O, Raso GM, et al. Further evidence for the involvement of prolactin in the inflammatory response. *Life Sci* 1993;53(6):PL105–10.