Inflammatory bowel disease and breastfeeding

Crohns Disease and Ulcerative Colitis

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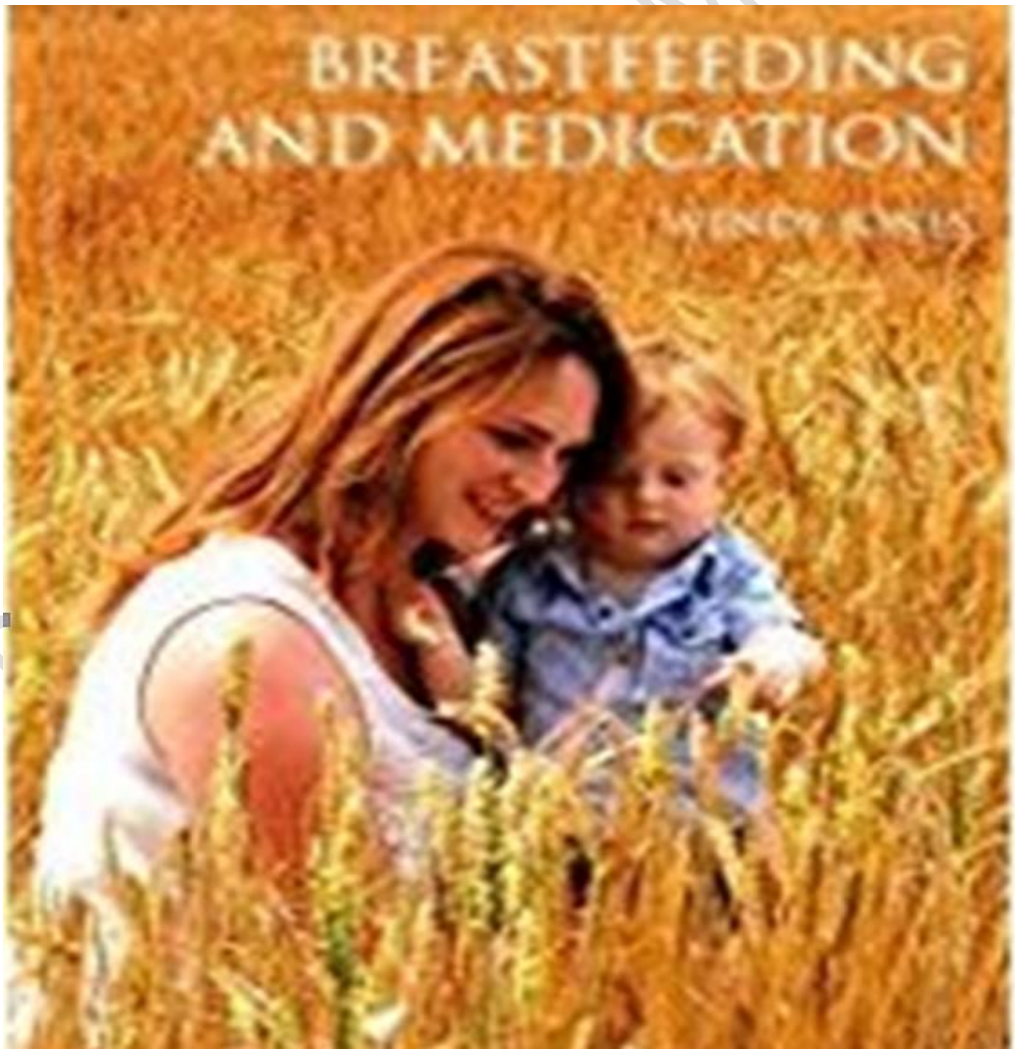

Contents

Inflammatory Bowel Disease and Breastfeeding

Inflammatory bowel disease (IBD) describes two conditions: ulcerative colitis (UC) and Crohn's disease (CD). They are long-term conditions that involve inflammation of the gut. Ulcerative colitis only affects the colon (large intestine). Crohn's disease can affect any part of the digestive system, from the mouth to the anus. People of any age can get IBD, but it is usually diagnosed between the ages of 15 and 40. There appears to be a genetic predisposition which is increased by early exposure to formula milk.

Symptoms of IBD include pain or spasms in the tummy, recurring or bloody diarrhoea, weight loss, extreme tiredness. It is estimated 1 in 5 people with ulcerative colitis have severe symptoms that do not improve with medication. In these cases, surgery may be necessary to remove an inflamed section of large bowel (colon). Around 60-75% of people with Crohn's disease will need surgery to repair damage to their digestive system and treat complications of Crohn's disease.

Association of IBD with feeding method as an infant

Whorwell et al. (1979) studied 57 patients with IBD and matched controls. He found that 29.9% of the patients had been artificially fed compared with 11.8% of controls, a statistically significant difference. He did not find a similar difference in patients with CD but did find significantly different incidences of early gastroenteritis in the first six months of life. He hypothesised that a pathogenic infection occurred that persisted and manifested as CD in later life. Whorwell et al. suggested that either bottle feeding was harmful or that breastfeeding is protective, possibly due to sensitisation to cow's milk proteins in early life, due to increased permeability to macromolecules. He also suggested that artificial feeding may alter bacterial flora at a time when sensitisation to bacterial antigens may occur.

There is a higher chance of developing IBD if there is a first-degree relative with the condition. Patients with IBD have a 5% risk of having a child who develops IBD. If both parents have the condition the risk rises to 35%. However, in only 45% of monozygous twins do both develop IBD and fewer in dizygotic twins. Environmental risk factors for IBD identified include smoking, diet, vitamin C consumption and the use of the oral contraceptive for females.

The incidence of diarrhoeal disease in the first six months of life seems to increase the risk of developing both CD and UC (Koletzko et al. 1989). Similarly, recurrent respiratory infections were significantly more common in UC and CD patients than matched controls, and patients with CD were more likely to have taken antibiotics. Breastfeeding is known to lower the incidence of gastrointestinal disease and respiratory tract infections and may therefore be expected to prevent these influences on the development of IBD.

In a meta-analysis of 17 articles Klement et al. (2004) found evidence that supported the hypothesis that breastfeeding is associated with a lower risk of developing both CD and UC, although few studies were of good quality and data on the duration and exclusivity of breastfeeding were lacking

or limited in all studies. All but two studies were retrospective, case-controlled studies so therefore subject to recall bias. However, the latent period for the development of IBD makes prospective studies difficult. Launer et al. (1992) have demonstrated the high accuracy of recall of breastfeeding duration by mothers up to 18 months after delivery but, in many of the studies analysed by Klement et al. (2004), data was collected after many years.

Xu et al. (2017) performed a systematic search and concluded that breastfeeding in infancy protects against CD and UC with the greatest benefit being with 12 months' breastfeeding duration.

Smoking and IBD

Corrao et al. (1998) studied 819 cases of IBD diagnosed between 1989 and 1992 (594 with UC and 225 with CD). He found that being a former smoker increased the odds ratio for UC whilst being a current smoker increased the odds ratio for CD by 1.7. For females, using the oral contraceptive increased the risk for CD but had no effect on UC risk. Lack of breastfeeding in infancy accounted for the highest proportion of CD in females in later life (odds ratio UC 1.5, CD 1.9). However, the data collected on breastfeeding was minimal or none, with no account taken for duration or exclusivity. Other factors investigated included limited physical activity, dietary factors, previous diseases, e.g., psoriasis, early infections, absence of appendectomy, alcohol intake, contact with animals, but the results of these investigation were conflicting.

Infant Feeding choices for the mother with IBD

Kane and Lemieux (2005) studied 122 women with IBD who had delivered in the previous five years. Only 44% had breastfed their babies. The reasons cited for choosing to formula feed included recommendation by the caring physician, fear of the safety of medication reaching their baby, as well as personal choice. Of the women with CD, only 29% chose to breastfeed, with a median duration of eight months (3–14 months). Of the population in the study who breastfed (54), 43% (23) experienced a postpartum flare, but when adjusted for medication cessation this was not statistically significant. Factors associated with a flare in the postpartum period (defined as an increase in disease activity within eight months of delivery) were hypothesised as discontinuation of medication, resumption of smoking and a possible significant change in hormones.

More women with CD expressed a desire to stay on their medication following delivery, fearing a flare, and therefore choosing not to breastfeed. Of the 30% who experienced a flare, 64% had been breastfeeding in the month before development of symptoms but 74% had chosen to stop their medication. The drugs most frequently cited were mesalamine and azathioprine. At the time of the study 60% of women in the general population were initiating breastfeeding.

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Transfer of medication into breastmilk

There is no cure for IBD , so the aim of treatment is to prevent flares and control symptoms.

In looking for medication compatible with breastfeeding the important factors are:

- The oral bio-availability of a drug: if a drug has zero oral bioavailability it cannot be absorbed by the baby from breastmilk
- The half-life of the drug: it takes 5 half lives to reach a steady state after which timing the drug with respect to feeds has no relevance. It takes 5 half lives for a drug to leave breastmilk.
- The plasma protein binding (PPB): the higher the plasma protein binding of a drug the less is free to pass into milk
- The milk plasma ratio: this ration needs to be less than 1, a level in excess of this suggests that the drug concentrates in milk and is less compatible with breastfeeding as it may indicate an active transfer
- The extent to which the drug undergoes first pass metabolism; limits level able to pass into milk
- Relative infant dose: this is a term used by experts on the transfer of drugs into breastmilk and a level below 10% is regarded as compatible with normal breastfeeding.
- Molecular weight: drugs with large metabolic weights generally have low oral bioavailability

We also need to consider the stage of the lactation. Drugs pass freely into breastmilk in the first few days after the birth when the inter-cellular gaps are wide open to facilitate the passage of immunoglobulins to protect the baby. The maturity of the baby is also important. A new-born baby has incomplete hepatic and renal function so may not be able to metabolise drugs as readily as an older child. If a drug is licensed for use in children the amount passing through milk will generally be lower than that which could be given directly.

Medication and IBD

Mesalamine/ mesalazine: be alert for watery diarrhoea. Negligible amounts in milk. Relative infant dose 0.12% - 8.76%, PPB 55%, oral bioavailability 20-40%

Sulfasalazine - be alert for bloody diarrhoea. licensed for use in children > 2 years

Balsalazide: absorbed in colon does not gut and broken down to mesalazine. Be alert for watery diarrhoea

Olsalazine –Monitor for watery diarrhoea

Immunosuppressants:

Prednisolone - 40mg is compatible with breastfeeding, short term higher doses are suitable. With long term higher doses wait 4 hours before breastfeeding to minimise transfer to baby but rarely is this necessary as dose is unusual

Azathioprine: Azathioprine is an immunosuppressive anti-metabolite. It is converted to mercaptopurine in the body. It has a corticosteroid-sparing effect and is widely used to produce and maintain remission in IBD, as well as conditions such as lupus and rheumatoid arthritis. Traditionally, breastfeeding by mothers have been discouraged from continuing to breastfeed if taking azathioprine because of the theoretical risks of infant bone marrow suppression, susceptibility to infection, growth retardation and pancreatitis.

According to recent research (Gardiner et al. 2007) breastfeeding need not be withheld in infants whose mothers are taking azathioprine. Gardiner et al. studied four mothers taking azathioprine. The metabolites 6-MP and 6-TGN were undetectable in neonatal blood and no clinical signs of immunosuppression were observed in the infants. Similarly Moretti et al. (2006) studied four babies and measured levels of 6-MP in breastmilk and neonatal blood for drug levels, white cell and platelet counts. Levels of metabolites were below the level of detection in the neonates and no clinical signs of immunosuppression were observed. Sau et al. (2007) studied ten women and similarly found no immunosuppression. Women taking azathioprine should therefore not be discouraged from breastfeeding.

It is licensed to be given to children over the age of 2 years at a dose of 2 mg per day initially for severe UC and CD. Relative infant dose is quoted as 0.07% to 0.3% (Hale 2017 online access).

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Mercaptopurine – metabolite of azathioprine. No studies on this drug alone but from azathioprine data levels in milk appear low.

Biologicals

Infliximab is a large molecular weight antibody and preliminary results suggest it is too large to pass into breastmilk and it is not orally bio-available. It is distributed primarily in the vascular compartment and has a terminal elimination half-life of 8 to 9.5 days. Infliximab is usually either not detectable in breastmilk or detectable at very low levels. Absorption of the drug from milk by the infant is minimal. Follow-up of infants exposed in utero and breastfed during maternal infliximab therapy have found no adverse effects and normal development. The measurement of minute concentrations in the milk of some women raises the possibility of local immune suppression in the gastrointestinal tract, but levels were not high enough to be of concern for systemic immunosuppression (LactMed)

It is suggested that use by a mother should not preclude breastfeeding based on this data (Peltier 2001; Forger 2004; Mahadevan 2005; Basilisks 2006).

Compatible with breastfeeding due to poor bio-availability

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- https://www.ncbi.nlm.nih.gov/m/pubmed/29857090/

Adalimumab - molecular weight 148,000. Poor oral bioavailability, relative infant dose 0.12%

Adalimumab is a recombinant human monoclonal TNF antibody that binds specifically to TNF- α. Elevated levels of TNF are found in the affected tissues of patients with CD and UC. It is used where there is no response to conventional treatment or relapse with infliximab (Wasan).
Adalimumab has a low oral bio-availability, a half-life of 2 weeks, a molecular weight of 148,000. It is likely that any small amounts in milk are destroyed in the baby's gut. Two infants of women who took adalimumab 40 mg subcutaneously during lactation were followed until 14.5 and 15 months of age. No adverse reactions were found in the infant to be attributed to exposure of the drug in breast milk. Both infants were reported to have met all developmental milestones (Fritzsche 2012). BNF however states that it should be avoided by breastfeeding mothers and that the manufacturer advises it should be avoided for at least 5 months after last dose. Earlier information recommended that infliximab should not be used in a breastfeeding mother until 6 months after the last dose.

Compatible with breastfeeding due to poor bio-availability and hence low-level absorption by the infant.

- Wasan SK, Kane SV. Adalimumab for the treatment of inflammatory bowel disease. Expert Rev Gastroenterol Hepatol. 2011 Dec;5(6):679-84.
- Fritzsche J, Pilch A, Mury D, Schaefer C, Weber-Schoendorfer C. Infliximab and adalimumab use during breastfeeding. J Clin Gastroenterol 2012;46(8):718-19.
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Golimumab - molecular weight 150,00. Limited oral bioavailability

Golimumab is a human monoclonal antibody to TNF α with similar activity to others in this class/. It is used to treat severe UC in patients who have shown an inadequate response to other treatments and/or are corticosteroid dependant.

The absolute bio-availability is 53%, the terminal half-life is 2 weeks. The BNF recommends that the manufacturer advises against breastfeeding for 6 months after use as it passes into milk in animal studies. However, because golimumab is a large protein molecule with a molecular weight of about 150,000, the amount in milk is likely to be very low and absorption is unlikely because it is probably destroyed in the infant's gastrointestinal tract (Nielsen 2014, Nguyen 2016, van der Woude 2015, Mahadevan 2017,).

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Certolizumab - molecular weight 149,100. Poor oral bioavailability, relative infant dose 0.04% - 0.3%. Licensed for use in breastfeeding

A study of 17 breastfeeding women, more than 6 weeks postpartum, evaluated the use of certolizumab in lactation.[Clowse] Sixteen women received certolizumab 200 mg every 2 weeks, and 1 received 400 mg every 4 weeks subcutaneously). Samples were collected at steady state every two days from day 0 to 14 and day 28 in the one patient receiving doses every 4 weeks. Breast milk samples from 4 of 17 women were undetectable throughout the dosing interval. Thirteen of 17 subjects had measurable levels in milk (peak 0.076 µg/mL) throughout the dosing interval. Fifty-six percent of all samples taken were below the limit of quantification. The estimated ADID ranged from 0 to 0.0104 mg/kg/day; median estimated ADID was 0.003503 mg/kg/day Using the Cave, the RID ranged from 0.04% to 0.35% while the median RID= 0.15%. Interestingly, certolizumab was below limit of quantitation in 56% of maternal milk samples. This study followed the breastfed infants for up to 5 weeks post maternal dose, and only one reported infant adverse event (nasopharyngitis) which was considered attributable to the medication. The milk levels found in this study are probably far too low to impact an infant.

In a separate study, plasma certolizumab pegol concentrations were collected 4 weeks after birth in 9 breastfed infants whose mothers had been currently taking CIMZIA (regardless of being exclusively breastfed or not). Certolizumab pegol in infant plasma was not measurable i.e., below 0.032 mcg/mL.[manufacturer information]

These levels in milk are probably too low to produce clinical effects in a breastfed infant.

- Clowse ME, Förger F, Hwang C, Thorp J, Dolhain RJ, van Tubergen A, Shaughnessy L, Simpson J, Teil M, Toublanc N, Wang M, Hale TW. Minimal to no transfer of certolizumab pegol into breast milk: results from CRADLE, a prospective, postmarketing, multicentre, pharmacokinetic study. Ann Rheum Dis. 2017 Nov;76(11):1890-1896.

Live vaccines in the babies of women taking immunosuppressants

The Torento consensus statement also suggested that live vaccinations are not recommended within the first 6 months of life in the offspring of women who were on anti-TNF therapy during pregnancy. Since anti-TNF drugs are very poorly bio-available this seems difficult to justify as the baby is not immune compromised. However, if live vaccinations e.g. rotavirus are used then the mother with IBD should use precautions like wearing gloves when changing the baby's nappy.

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Colonoscopies

Most patients with IBD will have to undergo periodical colonoscopies. There is no reason to interrupt breastfeeding during preparation for the procedure or following sedation using midazolam, fentanyl or mannitol. The mother can continue to breastfeed as normal but should ensure adequate hydration with appropriate fluids. Many mothers worry that not eating for 24 hours will reduce their milk supply. Fasting does drop the supply a small amount for some women but frequent feeds seem to overcome problems

- Mitchell J, Jones W, Winkley, Kinsella SM Guideline on anaesthesia and sedation in breastfeeding women 2020. Guideline from the Association of Anaesthetists https://associationofanaesthetists-publications.onlinelibrary.wiley.com/doi/full/10.1111/anae.15179

Bowel prep

- Macrogol e.g. Movicol®, Laxido®, KleanPrep ®; poorly absorbed from GI tract
- Polyethylene glycol- electrolyte solution. poorly absorbed from GI tract https://www.ncbi.nlm.nih.gov/books/NBK536694/
- Sodium picosulfate (Picolax®) is not absorbed from the gastrointestinal tract, and its active metabolite, which is absorbed, is not detectable in breastmilk. Breastfeeding can continue as normal.
- Senna; In one study of 23 women who received Senokot none was detectable in their milk Of 15 mothers reporting loose stools, two infants had loose stools (Werthmann 1973). However, in a randomized, double-blind trial comparing Senokot tablets to placebo, of the women in the study, 126 breastfed their infants and took senna while 155 control mothers breastfed their infants. There was no difference in the percentages of infants in the active and control groups with loose stools or diarrhoea (Shelton 1980).
    - Werthmann MW Jr, Krees SV. Quantitative excretion of Senokot in human breast milk. Med Ann Dist Columbia. 1973;42:4-5.
    - Shelton MG. Standardized senna in the management of constipation in the puerperium. A clinical trial. S Afr Med J. 1980;57:78-80.
    - Phosphate enema (Fleet®); Sodium phosphate is a saline laxative which sucks water into the lumen of the bowel. Whilst some phosphate may get into the plasma, it is very unlikely to change the levels in milk. The oral bioavailability is zero to 20%. Use of phosphate enemas should not require interruption of breastfeeding
- Bisacodyl (Dulcolax ®) oral bioavailability <5%

MRI scans and breastfeeding

A contrast medium containing gadolinium is frequently used. It is not radioactive and is given by intra venous injection into the arm. The gadolinium will be excreted from the body through the kidneys within 24 hours. For this reason, it is often suggested that mothers should pump and dump their breastmilk during this time.

The Summary of Product Characteristics (SPC) of ProHance states that "At clinical doses, no effects on the infant are anticipated due to the small amount excreted in milk and poor absorption from the gut. Continuing or discontinuing breast feeding for a period of 24 hours after administration of ProHance, should be at the discretion of the doctor and lactating mother. (https://www.medicines.org.uk/emc/product/1387/smpc).

The Royal College of Radiologists (RCR), the American College of Radiology (ACR) and the European Society of Urogenital Radiology (ESUR), The Royal Australian and New Zealand College of Radiologists (RANZR) note that the available data suggest that it is safe to continue breast-feeding after receiving intravenous contrast.

Oral absorption is minimal, with only 0.8% of gadopentetate being absorbed. (Lactmed, Hale). Ferris and Goergen confirmed that the amount received by the baby is so small it is not thought to represent any danger to the child.

Webb et al (2005) carried out an extensive literature review on the use of contrast media in pregnancy and lactation. They drew up guidelines which were presented and discussed at a European Symposium. They concluded that "only tiny amounts of iodinated or gadolinium-based contrast medium given to a lactating mother reach the milk, and only a minute proportion entering the baby's gut is absorbed. The very small potential risk associated with absorption of contrast medium may be considered insufficient to warrant stopping breastfeeding for 24 hours following either iodinated or gadolinium contrast agents". This is supported by Chen (2008).

Adverse events to gadolinium : A small number of patients (1-5%) who are given gadolinium as part of the MRI scan, may experience headache, nausea or dizziness but these effects generally pass within a few minutes of the injection. There is no evidence that the breastfed baby experiences any such effects as a result of exposure through breastmilk.

Brand Names : gadoterate (Dotarem®); gadodiamide (Omniscan®); gadobenate (MultiHance®), gadopentetate (Magnevist®, Magnegita®, Gado-MRT ratiopharm®), gadoteridol (ProHance®), gadoversetamide (OptiMARK®), gadoxetate (Primovist®), gadobutrol (Gadovist®)

MRI Contrast and breastfeeding

Because of the very small percentage of gadolinium-based contrast medium that is excreted into the breast milk and absorbed by the infant's gut, we believe that the available data suggest that it is safe for the mother and infant to continue breast-feeding after receiving such an agent [Kubik-Huch]. Ultimately, an informed decision to temporarily stop breast-feeding should be left up to the mother after these facts are communicated. If the mother remains concerned about any potential ill effects to the infant, she may abstain from breast-feeding from the time of contrast administration for a period of 12 to 24 hours. There is no value to stop breast-feeding beyond 24 hours. The mother

should be told to express and discard breast milk form both breast after contrast administration until breast feeding resumes. In anticipation of this, she may wish to use a breast pump to obtain milk before the contrast-enhanced study to feed the infant during the 24- hour period following the examination."

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- The Royal Australian and New Zealand College of Radiologists (RANZR) 2018 (page 24)
- The European Society of Urogenital Radiology (ESUR) 2018. http://www.esur.org/fileadmin/content/2019/ESUR_Guidelines_10.0_Final_Version.pdf (Page 29)

- The American College of Radiology (ACR) www.acr.org/Quality-Safety/Resources/Contrast-Manual (Breastfeeding and iodinated contrast page 101) states that Gadolinium-Based Contrast Agents:

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Further information

Crohns and Colitis UK info@crohnsandcolitis.org.uk

https://www.facebook.com/groups/BreastfeedingIBD

https://breastfeeding-and-medication.co.uk/fact-sheet/infliximab-and-breastfeeding

https://breastfeeding-and-medication.co.uk/fact-sheet/azathioprine-and-breastfeeding

https://breastfeeding-and-medication.co.uk/fact-sheet/live-vaccinations-and-immunosuppressant-medication-taken-by-breastfeeding-mothers

https://breastfeeding-and-medication.co.uk/live-video-2/inflammatory-bowel-disease-and-breastfeeding-facebook-live

July 2021 *The information on this sheet is based upon my professional experience as a pharmacist with a specialised interest in the safety of drugs in breastmilk, supported by evidence from expert sources. However, I cannot take responsibility for the prescription of medication which remains with the healthcare professionals involved. I am happy to discuss the evidence by email wendy@breastfeeding-and-medication.co.uk*