Haematochezia and allergy in breastfed infants

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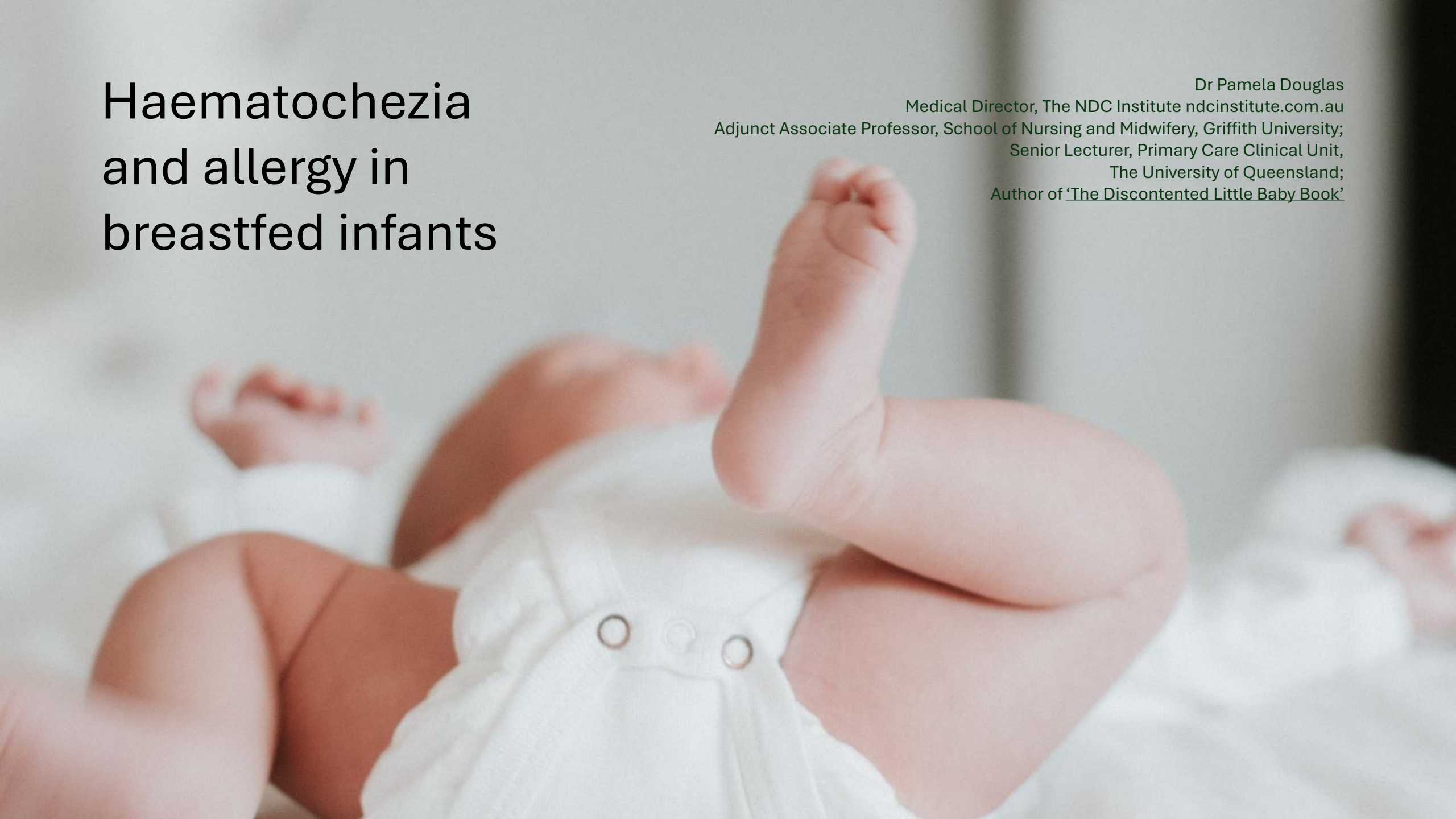

Prevalence of haematochezia

= blood in stool

Green stools are normal; mucous in stool is normal. Neither are signs of gut dysbiosis, clinically relevant inflammation, lactose overload or other gut abnormalities. [1-3]

- Most common in first 8 weeks of life, quite frequent in first 6 months
- Prevalence not clear – but common presentation

[1]Gustin et al 2018; [2]Huysentruyt et al 2019; [3]Vandenplas et al 2024

What is non-allergic benign infantile proctocolitis?

Term coined by Gelsomino et al 2021; previously had other names including idiopathic neonatal transient colitis[1]

Most common cause of small amounts of blood in stool

(e.g. Lazare et al 2020 n = 19 breastfed infants all tested positive with blood in stool after 3-weel elimination of diary and soy products, which eliminated FPIAP)

Presentation

- Under 6 months of age
- Small drops or streaks of blood in or on stool
- Doesn't continue more than 2 months
- Isn't getting worse

[1]Hwang and Hong 2013 ; [2]Lazare et al 2020; [3]Gelsomino et al 2021

What is non-allergic benign infantile proctocolitis?

Associated on endoscopy and colonoscopy (research studies) with mild and temporary inflammation in distal colonic or rectal mucosa but ***NOT*** elsewhere in gut.
No signs of immune cells indicating allergy in blood stream.
?Low grade viral infection

Exclude

- Anal fissure
- Swallowed blood syndrome in first days of life?[1]

[1]Lin et al 2022

Management of non-allergic benign infantile proctocolitis

- ***Wait and watch for two months***
- Frequent flexible breastfeeds
- No investigation required
- Not allergic or related to food proteins (either breast milk proteins or from solids)
- Reassure parents no link with IgE-mediated allergy (e.g. to solids) later on
- Deal with any co-presentations separately:
  - Unsettled infant behaviour
  - Benign vomiting (reflux)
  - Eczema
  - Weight gain concerns
- Review if bleeding worsens or persists at two months

Arvola et al 2006

- Microvillus layer had virus particle aggregates (not found in faeces) in 8 of 32 in study of healthy infants with haematochezia

Wurm et al 2023

- During recruitment, more than half of healthy infants presenting with rectal bleeding were found to have a gut virus or pathogen on stool analysis (and eliminated from study)

- 14 infants with rectal bleeding (av age 11.1 wks) cf 55 controls (av age 12.7 wks)

- Rectal bleeding infants
  - Less bifidobacterium and other microbiome changes cf non-bleeding infants
  - Aggregates of eosinophils in colonic mucosa

- After 4 weeks cow's milk elimination diet, microbiome of infants with rectal bleeding partially changed to look more like microbiome of non-bleeding, but these changes in microbiome might have occurred regardless of diet

- No explanation for how an ingested protein causes an allergic reaction in distal colon only without other gut or immune cells in blood stream being affected.

Non-IgE-mediated allergies in breastfed infants

1. *Constipation*
2. *Coeliac disease*
3. *Cow's milk-induced iron deficiency anaemia*
4. **Food protein-induced allergic proctocolitis**
5. **Food protein induced enterocolitis syndrome**
6. Anaphylaxis

Allen et al 2022; Banerjee et al 2023;
McWilliam et al 2023; AL-lede et al 2023

Food protein induced allergic proctocolitis

Acknowledged to be overdiagnosed and overtreated.
Only 15-40% infants with rectal bleeding are finally diagnosed with FPIAP after diagnostic dietary intervention.
Partial or exclusive breastfeeding protects against true FPIAP.
Usually outgrown by 1-3 years of age.
Not associated with eosinophilic oesophagitis or later inflammatory bowel disease.
Histology shows marked eosinophils and degranulation in rectosigmoid colon close to lymphoid nodules.
No signs of immune cells indicating allergy in blood stream.

Presentation

- Older than 6 months of age
- Pink or red stool *OR*
- Amount of blood is increasing over time *OR*
- Has gone on for two months without stopping

Arvola et al 2006; Miceli et al 2018; Mennini et al 2020; Gelsomino et al 2021; McWilliam et al 2023; Wurm et al 2023; Silvatore et al 2024;Tran et al 2024; Vandenplas et al 2024

Management of food protein induced allergic proctocolitis

- Cow's milk protein elimination diet for 4 weeks
- High cross-reactivity of cow's milk protein with goats and sheep's milk proteins (relevant to formula-fed infants in particular)
- No reason to eliminate soy, egg and wheat as these protein allergies are[1]
  - Uncommon
  - Prevalence and relevance remain poorly established
- Resolution of haematochezia is diagnostic of FPIAP
  - Usually within a few days but up to within a fortnight

[1]Allen et al 2022

Risks of overdiagnosis and overtreatment of food protein induced allergic proctocolitis

- Burden of eliminating food stuffs
- Unnecessary family stress
- Failure to identify underlying causes of infant behaviour
- Breastfeeding mother loses benefits of dairy's
  - Probiotic
  - Calcium
  - Vitamin D benefits of dairy
- Increased risk of cow's milk allergy later on

Tran et al 2024 [case series]

5 infants

- Rectal bleeding diagnosed with FPIAP
- Placed on elimination diets of unknown duration (either maternal elimination diet if breastfeeding or by formula change)
- Developed persisting cow's milk allergy down the track

EITHER

Infant rectal bleeding is always FPIAP, associated with persisting cow's milk allergy

OR

Cow's milk elimination diets, which are not indicated if non-allergic benign infantile proctocolitis, result in persisting cow's milk allergy[1].

[1] McWilliams et al 2023

Eczema is a common inflammation of infant skin

- If small or moderate patches, no reason to consider allergy
- Consider allergy if very severe and extensive eczema (only), trial elimination diet

Distal colon or rectal mucosa commonly inflamed resulting in bleeding in early infancy

- If small or moderate patches, no reason to consider allergy
- Consider allergy if severe and extensive resulting in substantial or worsening haematochezia, trial elimination diet

‘Cluster of signs’ concept lacks evidence base
→ drives overdiagnosis and overtreatment of allergy in infants

The following signs, alone or in a cluster, are not linked with non-IgE mediated allergy infants

- Feeding aversion: fussy during feeds or “in pain with feed”
- Colic (sometimes told that if infant is fussy after 16 weeks more likely to be allergy)
- Reflux
- Frequent vomiting
- Poor weight gain or failure to thrive
- Loose mucousy stool
- Eczema – rarely driven by food

Non-IgE mediated allergy in breastfed infants: busting myths

Don’t diagnose non-IgE mediated allergy by ‘cluster’ of symptoms

- Not evidence-based clinical practice
- ‘Clusters’ not linked with haematochezia
- Directly causes overdiagnosis, overtreatment, and increased allergy prevalence[1]

Don’t advice breastfeeding mothers to look for pattern of unsettled infant behaviour in 12-24 hour period after ingestion of dairy/soy/eggs/wheat etc

- Not evidence-based clinical practice
- Exacerbates maternal anxiety
- Directly causes overdiagnosis, overtreatment, and increased allergy prevalence[1]

[1] McWilliam et al 2023

Food protein induced enteropathy syndrome

- Sick infant
- Predominantly formula fed infants
- Rare in breastfed babies but can occur e.g. when breastfed baby takes formula or commences solids which contain cow's milk protein
- No diagnostic test

Acute FPIES

- Vomiting 1-4 hours after feed
- Pallor, sweatiness, clamminess, lethargy
- Diarrhoea
- Hypovolemia (shock)

Requires emergency medical care

Chronic FPIES

Intermittent vomiting
Frequent diarrhoea
Abdominal distention
Pallor after feeds
Hypotonia, lethargy
Dehydration
Faltering growth
Protein-losing enteropathy

- altering growth
- Low serum albumin
- Oedema

Requires prompt or urgent medical care
If over 6 months of age can use soy-based formula

Allen et al 2022; Banerjee et al 2023; McWilliam et al 2023; AL-lede et al 2023

- Most constipation is not CMA
  - Breastfed babies may not pass stool for many days at a time.
  - Constipation and a true gastro-oesophageal reflux disease in an older child may be classified as food protein-induced dysmotility disorders.

- FPIAP is not associated with vomiting, diarrhea or failure to thrive – but these are signs of food-protein-induced enteropathy syndrome.

- If infant is formula fed and has persisting visible blood in the stools, advise extensively hydrolysed formula.

IgE mediated cow's milk allergy in breastfed infants

- Typically occurs with direct infant ingestion of dairy
- Skin signs (urticaria, severe eczema, erythema)
- Hayfever
- Reactive Airways
- Vomiting two hours after takes in formula or dairy
- Swellng (angioedema)
- Accompanied by positive skin prick test or serum IgE in older infants
- Mix of non-IgE and IgE mediated CMA possible

Researchers demonstrate that there are almost no circumstances where breastfeeding women should eliminate dairy from their diet

- Cow's milk allergy prevalence is estimated at 0.4%-0.8% in exclusively breastfed infants prior to introduction of any breast milk substitutes or solid foods
- In about 2% of infants otherwise
- Cow's milk proteins don't usually occur at high enough levels in breast milk to trigger allergic reactions in babies regardless of how much dairy mother consumes
- The only absolute medical contraindication to breastfeeding or use of donor breastmilk is classic galactosaemia.

Allen et al 2022; Munblit et al 2020; McWilliam et al 2023

Researchers demonstrate that there are almost no circumstances where breastfeeding women should eliminate dairy from their diet

Munblit et al 2020

- 99% of babies and toddlers with true cow's milk allergy tolerate breast milk from a woman who is consuming dairy products without having an allergic reaction.

McWilliam et al 2023

- Concentrations of cow's milk proteins in breast milk vary widely, irrespective of the amounts consumed by the mother and the timing of consumption.
- Beta lactaglobulin (cow's milk protein) detected in about half of samples regardless of cow's milk consumption.
- It is difficult to consume enough dairy for beta lactaglobulin to reach a significant level in breast milk.

Even in the case of a true cow's milk allergy, maternal elimination diet should not be a standard recommendation for breastfeeding babies.

If maternal elimination diet is indicated, Allen et al 2022 propose that goat and sheep milk protein should also be avoided due to cross-reactivity, and that re-introduction would occur if a two-week trial does not result in resolution of symptoms, or two weeks after symptoms have resolved.
Soy can be used in breastfed infants with CMA.

Allen et al 2022; Munblit et al 2020; McWilliam et al 2023

Allen et al 2022 find that cross-reactivity between cow's milk and soy-based formulas is low, so infants with cow's milk allergy and food protein induced enteropathy syndrome who are over six months of age could use soy-based formula.

Mehta et al 2022 demonstrate that volumes of specialised formula prescriptions have increased two-fold in the past twenty years in the UK, Australia and Norway, in the absence of increased prevalence of milk allergy.

- They propose that most infants prescribed specialised formula do not have milk allergy.

- They identify up to a ten-fold excess prescription rate relative to true rate of milk allergy.

- They observe that unnecessary specialised formula use increases consumption of free sugars (sich as glucose or sucrose, which substitute for the lactose found in breast milk and formula), risking dental decay and obesity in later life.

Lessons

Often substantial gap between evidence and consensus guidelines due to health system blind spots in care of breastfeeding women and their infants

Consensus guidelines require critical analysis going back to primary sources of research. Red flags are:

- Not consistent with evolutionary biology
- Appear to be driving overdiagnosis and overtreatment

Think critically about non-generalist medical specialists' interpretation of research (often – like all of us - not trained to critique studies, rely on consensus guidelines)

Complex primary care health problems and relevant research are most effectively analysed using lens of

- Complexity science (vs reductionism)
- Evolutionary biology
- Holistic, generalist clinical practice