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Case–control study of milk curd obstruction in newborn infants in a tertiary surgical neonatal intensive care unit

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This work has been presented at the Annual Scientific Meeting of the Perinatal Society of Australia and New Zealand, Christchurch, April 2024.

Received 19 June 2024
Accepted 12 September 2024

To cite: Walsh O, Anthony R, Wang Z, *et al*. *Arch Dis Child Fetal Neonatal Ed* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/archdischild-2024-327565

ABSTRACT

Background Milk curd obstruction (MCO), in which milk becomes inspissated, is a rare, serious, complication of preterm birth. Case reports implicate male sex and bovine-derived human milk fortifier (HMF) use as predisposing factors. We investigated this through a case–control study.

Methods MCO cases in the Starship Child Health neonatal database between 2008 and 2020 were matched with controls in a 1:2 ratio based on gestational age (±1 week), birth weight (±200 g) and date of birth (±1 month). Data were analysed using the Student's t-test, Mann-Whitney U-test or χ^2 test as appropriate. Data are median (IQR) or n (%).

Results Of 20 MCO cases, gestation was 26.1 (24.5–28.1) weeks, birth weight was 822 (713–961) g, 15 (75%) were male. 40 controls were well-matched for gestation (26.1 (24.8–27.9) weeks) and birth weight (849 (690–1066) g) but only 18 (45%) were male (p=0.05). MCO occurred at 21 (15–33) days; 6 (30%) cases died compared with 3 (7.5%) controls (p=0.06). HMF was commenced at 243 (150–309) hours in cases and 224 (172–321) hours in controls (p=0.95); full-fortification (manufacturer's recommended dose) was achieved in 8 (40%) cases and 27 (68%) controls (p=0.08). In cases, MCO occurred 10 (7–17) days after commencing HMF. Medically/surgically-managed gut pathology occurred in 7 (35%) cases prior to MCO but in no controls (p<0.001).

Conclusions Our data support male sex but not HMF use as a predisposition to MCO. Evidence of prior medical/surgical gut pathology may be a premonition for MCO; however, further research is required to confirm this.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Milk curd obstruction (MCO) has been documented since the late 1930s. Although rare, it has been reported in at least 40 infants over the past two decades causing enteral feeding cessation, bowel necrosis and short bowel syndrome.

WHAT THIS STUDY ADDS

⇒ This study uses a case–control approach rather than case series and supports male sex as a likely predisposing factor. However, our findings do not support bovine-derived multicomponent fortifier use as a risk factor.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings challenge the reported association between bovine-derived multicomponent human fortifier use and MCO that may mitigate concerns; however, further research into the causes of this rare but serious condition is needed.

INTRODUCTION

Milk curd obstruction (MCO) is a rare complication in neonates in which enterally-fed milk becomes inspissated, causing bowel obstruction. Milk inspissation was first reported in the late 1930s in a comprehensive literature review of cases presenting with bezoars and concretions in adults.[1] Reports of cases in infants appeared in the 1950s and 1960s as the use of infant formula derived from cow's milk began to increase.[2 3] With improved formula composition and feeding strategies, the reported incidence decreased substantially thereafter but case reports and case series, the largest containing 10 infants, in the last two decades indicate a resurgence of cases reporting at least 40 infants.[4–9] MCO remains of concern because its development may cause cessation of enteral feeding, bowel necrosis, need for formation of a stoma and short bowel syndrome following surgical resection of non-viable bowel. The underlying cause(s) of MCO remain unknown but these case series and reports have pointed towards an increased incidence in male infants and a potential association with the fortification of the mother's own expressed breast milk (EBM) with bovine-derived multicomponent human milk fortifier (HMF). However, the evidence to substantiate this hypothesis remains inadequate. We therefore undertook a case–control study in an attempt to systematically identify potential exposures and antenatal, perinatal and postnatal risk factors that may elevate the risk of MCO.

METHODS

A retrospective observational case–control study using data from a quaternary neonatal intensive care unit (NICU) and neonatal surgical centre at Starship Child Health, Auckland, New Zealand. Cases were infants from 2008 to 2020 identified from the prospectively maintained NICU database with medical records showing a clinical,

radiological, surgical or histopathological diagnosis of MCO. Infants with clinical and/or surgical diagnosis of MCO but who also had a histopathological finding of necrotising enterocolitis (NEC) were included due to ongoing debate about the cause-and-effect relationship between MCO and NEC.[10]

Two controls were matched to each case based on gestational age (±1 week), birth weight (±200 g) and date of birth (±1 month) to account for factors related to feeding, degree of prematurity/growth restriction and changes in neonatal care practice over time.

Data were collected from electronic medical records and stored in an unidentifiable form to protect participants' privacy. Participants were assigned unique 6-digit study numbers and data entry into a REDCap (Research Electronic Data Capture) database was performed twice to minimise transcription errors.

Maternal weight at booking was assessed using body mass index (BMI) (kg/m^2) and categorised according to the National Institute for Health and Care Excellence guidelines (underweight BMI<18.5 kg/m^2; normal weight 18.5–24.9 kg/m^2; overweight 25–29.9 kg/m^2; obese 30–39.9 kg/m^2, and morbidly obese≥40 kg/m^2).[11] Evidence of gut pathology requiring medical and/or surgical management prior to the MCO diagnosis was collected from the medical notes and was grouped into NEC, spontaneous intestinal perforation, congenital anomaly of the gastrointestinal tract, inguinal hernia(e), septic ileus and meconium ileus; medication data were retrieved from the medication charts.

Continuous data were assessed for distribution and transformed as appropriate. Student's t-test was used for continuous data while non-parametric data were analysed using the Mann-Whitney U test. Categorical data were assessed with χ^2 or Fisher's exact test. Logistic regression was used to account for potential confounders. The level of statistical significance was set at 5% without correction for multiple comparisons as the study aimed to generate hypotheses and identify potential contributing factors to MCO. Quantitative variables were treated as continuous data whenever possible; growth measurements were converted to z-scores using the Fenton and Kim growth charts.[12]

RESULTS

We identified 20 cases of MCO between 2008 and 2020 and 40 matched controls. Cases and controls were well matched (table 1). Median birth weight was 823 and 849 g for cases and controls, respectively, and median gestational age was 26 weeks for both groups (table 1). Almost all infants in both case and control groups received at least some antenatal steroids (table 1). The proportion of males among cases was 75% compared with 45% in controls; 30% of cases died compared with 7.5% of controls (p=0.05, table 1).

Time to first feed (all infants received EBM) and time to the first addition of fortifier were similar between cases and controls (table 2). In cases, MCO occurred at a median age of 21 days (IQR 15–33). 40% of MCO cases received HMF (as per manufacturer's instructions) compared with 68% of controls (p=0.08, table 2); use of half-dose fortification was uncommon in cases (5%) and controls (10%). The median time between the addition of fortifier and the onset of MCO was 10 days (table 2). Enterally given oral medication use was not different between cases and controls (table 3).

Abnormal ultrasound and abdominal radiograph findings were found exclusively in the case group. Surgery for MCO was required in 15 (75%) cases with surgical findings consistent with MCO present in all of these; histological findings of MCO were reported in 6 of the surgical cases and histological findings of NEC were reported in 3. Gut pathology requiring medical or surgical management symptomatology prior to presentation with MCO was present in 7 (35%) cases prior to the episode leading to diagnosis of MCO but there was no gut pathology symptomatology in any of the controls at any time (table 2). Other clinical findings were not statistically significant (table 4).

Table 1 Baseline demographics for cases and controls

	Milk curd obstruction (n=20)	Controls (n=40)	P value
Mother's ethnicity			0.59
Māori	2 (10)	9 (23)	
Pacific Island	3 (15)	3 (8)	
Asian	5 (25)	9 (23)	
European	10 (50)	19 (48)	
Maternal age, years	34 (30–35)	31 (27–34)	0.09
Maternal weight category at booking*			0.19
Underweight	2 (10)	0 (0)	
Normal weight	7 (35)	21 (53)	
Overweight	7 (35)	7 (18)	
Obese	3 (15)	6 (15)	
Morbidly obese	0 (0)	2 (5)	
Diabetes mellitus			0.14
Type 1 DM	0	0	
Type 2 DM	0	0	
Gestational DM	0 (0)	7 (18)	
Fetal growth restriction†	3 (15)	1 (3)	0.10
PET/gestational hypertension	3 (15)	2 (5)	0.32
Gestation, weeks	26.1 (24.5–28.1)	26.1 (24.8–27.9)	0.89
Birth weight, g	823 (713–961)	849 (690–1066)	0.62
Birth weight, Z-score, mean (SD)	−0.12 (0.94)	0.20 (0.64)	0.12
Sex, male	15 (75)	18 (45)	0.05
Antenatal steroids‡			
Any steroid	20 (100)	38 (95)	0.80
Complete course	15 (75)	24 (60)	0.39
Magnesium sulfate complete	14 (70)	29 (73)	1.0
Intrapartum intravenous antibiotics			0.62
<4 hours prior to delivery	8 (40)	11 (28)	
>4 hours prior to delivery	10 (50)	24 (60)	
Not given	2 (10)	5 (12)	
Caesarean section	10 (50)	12 (30)	0.22
Active labour	11 (55)	30 (75)	0.20
Apgar score 1 min	4 (3–6)	5 (4–6)	0.12
Apgar score 5 min	7 (6–8)	8 (6–9)	0.33
Age when MCO occurred, (days)	21 (15–33)	–	
CRIB II score§	13 (9–14)	12 (9–14)	0.84
Died	6 (30.0)	3 (7.5)	0.05

Data are n (%), median (IQR) or mean (SD).
*Data were not available for one cases and four controls.
†Based on consensus criteria Beune *et al* [29]
‡Complete course of steroids: <7 days and >24 hours prior to delivery.
§CRIB II, Clinical Risk Index for Babies version II (a score based on mortality probabilities for gestation, sex, birth weight, admission temperature and base excess).[30]
Gestational DM, gestational diabetes mellitus; MCO, milk curd obstruction; PET, pre-eclamptic toxaemia; Type 1 DM, type 1 diabetes mellitus; Type 2 DM, type 2 diabetes mellitus.

Table 2 Enteral feeding data

	Milk curd obstruction (n=20)	Controls (n=40)	P values
Time to first EBM, hours	20 (15–49)	23 (11–39)	0.68
Received full fortification of breast milk feeds*	8 (40)	27 (68)	0.08
Received half fortification of breast milk feeds†	1 (5)	4 (10)	0.87
Age when HMF added, hours	243 (150–309)	224 (172–321)	0.95
Time between addition of fortifier and onset of MCO, days	10 (7–17)	N/A	
Age when feed volume 150 mL/kg/day	9 (9–14)	10 (9–11)	0.66
Ever on continuous enteral feeds	3 (16)	15 (39)	0.13
Age continuous enteral feed was started, days	23 (20–34)	17 (11–21)	0.15
Duration of continuous enteral feed, days	4 (3–9)	11 (10–19)	0.10
Preterm formula	4 (20)	4 (10)	0.42
Term formula	0 (0)	4 (10)	0.29
Time to first meconium, hours	20 (3–84)	14 (1–44)	0.36
Prior medically/surgically-managed gut pathology‡	7 (35)	0 (0)	2.007×10^{-4}

Data are n (%), median (IQR).
Comorbidities: Surgically and medically managed NEC (n=1), medically managed NEC and inguinal hernia (n=1).
*Fortifier added as per manufacturer's instructions.
†Fortifier added in half the recommended dose.
‡Prior medically-managed or surgically-managed gut pathology included NEC (n=2), spontaneous intestinal perforation (n=1 (colon)), congenital abnormality (n=0), meconium ileus (n=1), inguinal hernia (n=2, both bilateral and reducible) or septic ileus (n=1).
EBM, expressed breast milk; HMF, human milk fortifier; MCO, milk curd obstruction; NEC, necrotising enterocolitis.

DISCUSSION

Our findings support existing case reports and series that male infants have a predisposition to develop MCO.[13–15] As MCO is rare, numbers are small and the borderline statistical significance in this case–control study which is large compared with other reports, likely reflects the small sample size. The underlying mechanism for a probable increased disposition in males is unknown. The male disadvantage for neonatal morbidity and other morbidities is well established.[13–17] A 2018 meta-analysis of sex difference in mortality in preterm infants found that, of the 32 studies included, 26 studies showed an association between mortality and male sex.[18] There also is some evidence that males and females respond differently to certain treatments, including nutritional therapy.[17 19] We did not find any differences in oral medication therapy between cases and controls, suggesting that different medication for males and females is not a contributing factor. The mechanism behind sex-specific responses to therapeutic interventions is not well understood. Possible contributing factors include differences in the hormonal milieu which are present from fetal life and differences in the microbiome including in the terminal ileum, the most common site for MCO.[19–21] Sex chromosome-dependent hormonal and epigenetic mechanisms related to gut microbiome are postulated to be a contributing cause of male susceptibility or female resilience to certain disease states and subsequently may also relate to MCO development.[20 21]

Table 3 Enterally-given medications

	Milk curd obstruction (n=20)	Controls (n=40)	P values
Mycostatin	20 (100)	37 (93)	0.54
Probiotic	16 (80)	32 (80)	1.0
Oral caffeine	5 (25)	7 (18)	0.51
Vitadol C	3 (15)	6 (15)	1.0
Vitamin D drops (Puria)	2 (10)	4 (10)	1.0
Vitamin A	2 (10)	4 (10)	1.0
Oral sodium chloride	11 (55)	28 (70)	0.25
Ferrous sulfate	4 (20)	19 (48)	0.05
Dexamethasone	4 (20)	12 (30)	0.54

Data are n (%).

In contrast to previous reports, we did not find evidence of an association between the use of bovine-derived multicomponent human milk fortifier and the incidence of MCO. HMF is used routinely in many neonatal units to provide additional macronutrients and micronutrients including calories, protein, calcium and iron to support growth in preterm infants. There is an ongoing debate about whether bovine-derived HMF is a risk factor for NEC with small randomised controlled trials (RCT) indicating that an exclusive human milk-based diet but not mother's milk supplemented with HMF results in a lower incidence of NEC than a diet derived from bovine-derived milk.[22] However, a recent larger multicentre RCT comparing human milk-based fortification with bovine milk-based fortification in exclusively breast milk-fed extremely preterm infants found no difference in the composite outcome of NEC (≥stage 2), culture-proven sepsis and mortality (35.7% vs 34.5%).[23] The mechanism underlying the development of MCO is uncertain. There are documented cases of MCO which have found that the curd compositions are high in calcium and casein[5] that have proposed that an immature gastrointestinal system's inability to absorb the added macronutrients and micronutrients causes milk to coagulate.[5 7]

An interesting finding was that infants with MCO were more likely to have had medical or surgical management for presumed or actual gut pathology prior to the episode during which MCO was diagnosed, consistent with other case studies.[5 8 10] This finding suggests the importance of considering and investigating MCO in infants displaying signs of possible gastrointestinal obstruction without concurrent indications of NEC. Other case studies have expressed doubt that prior gut pathology directly increases susceptibility to MCO but have suggested that it enhances the likelihood of additional gastrointestinal complications.[5] The increased mortality could be related to the outcomes of these complications including perforation in the bowel wall and sepsis plus the operative mortality of MCO surgical interventions which is estimated at 6%.[5 20] However, these infants often exhibit other morbidities associated with prematurity

Table 4 In-hospital clinical characteristics of cases and controls

	Milk curd obstruction (n=20)	Controls (n=40)	P values
Type of ventilation			
CPAP	15 (75)	31 (80)	0.95
IPPV	18 (90)	29 (74)	0.19
HFOV	3 (15)	3 (8)	0.40
Highest MAP (cm H_2O) in first 24 hours	8 (7–10)	8 (7–10)	0.85
Inhaled nitric oxide	1 (5)	3 (8)	1.0
Intravenous antibiotics	19 (95)	33 (85)	0.40
Duration>36 hours*	12 (60)	24 (62)	1.0
Amoxicillin	18 (90)	36 (92)	1.0
Other antibiotic	3 (15)	6 (15)	1.0
Umbilical artery catheter	13 (65)	27 (69)	0.97
Hypotension requiring treatment†	5 (25)	11 (28)	1.0
Hypernatraemia‡ in first 2 weeks	12 (60)	22 (56)	1.0
Late onset sepsis§	10 (50)	28 (72)	0.17
Postnatal steroids	4 (20)	13 (33)	0.37
Dexamethasone duration	7 (6–8)	10 (6–12)	0.36
Hydrocortisone duration		2	NA
PDA¶	8 (40)	24 (62)	0.20
Medically treated	7 (35)	10 (26)	0.65
Surgically treated	0 (0)	0 (0)	NA
Hyperglycaemia**	4 (20)	10 (26)	0.75
Red blood cell transfusion	18 (90)	26 (67)	0.06

Data are n (%) or median (IQR).
*Unit policy is to discontinue antibiotics initiated for suspected sepsis after 36 hours if cultures are negative and there is no ongoing clinical concern.
†Hypotension requiring clinical management with either inotropes or fluid resuscitation.
‡Serum sodium concentration>145 mM.
§Defined as babies who required antibiotics for≥48 hours beyond 72 hours from birth for suspected sepsis.
¶Haemodynamically significant patent ductus arteriosus confirmed on echocardiography.
**Elevated blood glucose concentration requiring insulin therapy.
CPAP, continuous positive airway pressure; HFOV, high frequency oscillatory ventilation; IPPV, intermittent positive pressure ventilation; MAP, mean airway pressure; PDA, patent ductus arteriosus;

making it difficult to establish precise mortality rates specifically attributable to MCO.

Currently, plain abdominal radiography is the standard diagnostic modality for neonatal bowel conditions; however, its specificity is limited in differentiating various conditions, including MCO.[24] Typical radiological signs of MCO on plain radiographs include heterogeneous opaque masses with a distinctive appearance often surrounded by a black halo representing air.[25] MCO usually is a diagnosis of exclusion. While contrast enema studies have been employed in some cases, they are less beneficial for detecting MCO primarily because this condition most commonly affects the terminal ileum.[6] Thus, MCO can present a diagnostic challenge with clinical presentations mimicking that of NEC.[24] There is significant variability in diagnostic criteria for MCO nationally and internationally ranging from requiring intraoperative findings to only requiring clinical signs of bowel obstruction in babies receiving caloric fortification.[26 27] MCO is therefore likely under-reported as medical management may not be able to discriminate from NEC and when histopathology is present it often shows evidence of ischaemia. Further, MCO may be considered a consequence of NEC rather than a predisposing factor. To improve diagnostic accuracy, point-of-care abdominal ultrasound can be employed which in cases of MCO reveals homogeneous bright echogenicities within the intraluminal cavity facilitating the differentiation of MCO from NEC.[28] Integrating ultrasound findings with clinical and radiological findings may aid in the early diagnosis of MCO, prompting appropriate management and treatment strategies.[28]

Gastrografin enema has been reported as a therapeutic approach for MCO; however, the reported success of this procedure is variable and iatrogenic perforations have been reported.[20]

The strengths of this study are that, in comparison with existing literature, the numbers are large and we have undertaken a matched case–control approach rather than a case series. In addition, cases were ascertained from a prospectively-maintained database which ensures that we likely have captured most cases between 2008 and 2020 and have been able to rigorously match controls. However, we acknowledge that the numbers remain small given that MCO remains a rare complication. This makes determination of contributing factors challenging and also means the power of the study is limited. Thus, there is a possibility for type II error. Another potential weakness is that administration of HMF is a common practice in our NICU; hence, disparities between infants who received HMF and those who did not might introduce confounding variables for which we could not account. However, the control group exhibited a greater tendency to receive fortifier and a lesser propensity for prior gastrointestinal symptoms making this explanation unlikely. Given the retrospective nature of this study, complete case ascertainment is impossible to verify.

CONCLUSION

MCO is a rare complication that poses significant challenges in identifying the underlying cause. We found that male sex and prior symptomatology of gut pathology are apparent risk factors. However, we did not find evidence of an association or apparent link between the use of HMF and MCO.

Contributors The study was conceived by FHB and BEC and the protocol designed by FHB, BEC and RA. Data were collected by RA. OW analysed the data with statistical expertise provided by ZW. OW drafted the manuscript. All authors contributed to finalising the manuscript. FHB as guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Patient consent for publication Not applicable.

Ethics approval Ethical approval was granted by the New Zealand Health and Disability Ethics Committee (21/CEN/24) and locality approval by the Auckland District Health Board Research Review Committee (A+9188). Due to the study's retrospective nature, long time frame, likelihood of inclusion of infants who died and the rarity of milk curd obstruction, informed consent from participants was not sought. HDEC review approved this approach, recognising that obtaining consent likely would introduce significant bias through lack of complete case ascertainment due to drop-out through inability to trace families and/or lack of consent and may cause distress to families whose babies died.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement De-identified data will be available to researchers who provide a methodologically sound proposal with appropriate ethical approval, where necessary and following approval of the proposal by the Data Access Committee at the Liggins Institute. Data requestors will be required to sign a data access agreement before data are released. Request for access to data can be made to the Maternal and Perinatal Research Hub at the Liggins Institute, University of Auckland (researchhub@auckland.ac.nz<mailto:researchhub@auckland.ac.nz>).

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