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Prevalence and Health Outcomes of Functional Gastrointestinal Symptoms in Infants From Birth to 12 Months of Age

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ABSTRACT

Objectives: The aim of the study was to review published evidence and the opinion of practising clinicians on the prevalence and long-term health consequences of functional gastrointestinal symptoms in infants younger than 12 months.

Methods: PubMed was searched from inception to November 2014 to find articles reporting the prevalence and long-term health outcomes of infantile colic, regurgitation, functional constipation, functional diarrhoea, and dyschezia in infants younger than <12 months. A questionnaire was sent to practising clinicians worldwide, and a group of 15 international experts met to discuss the likely frequency and longer-term consequences of these symptoms.

Results: The literature search identified 30 studies reporting the prevalence of infantile colic (2%–73%), 13 that of regurgitation (3%–87%), 8 that of functional constipation (0.05%–39.3%), 2 that of functional diarrhoea (2%–4.1%), and 3 that of dyschezia (0.9%–5.6%). The studies varied in design, populations investigated, and definition of the symptoms. Questionnaires were received from 369 respondents. The experts agreed that the likely prevalences for colic, regurgitation, and functional constipation were 20%, 30%, and 15%, respectively. The limited data in the literature for functional diarrhoea and dyschezia suggest prevalences <10%. Infantile colic may be associated with future health problems in a subset of infants.

Conclusions: Functional gastrointestinal symptoms appear to occur in a significant proportion of infants younger than 12 months and may have an impact on future health outcomes. Prospective collection of data according to agreed criteria is needed to obtain more accurate estimates of the prevalence and consequences of these symptoms.

Key Words: constipation, dyschezia, functional diarrhoea, functional gastrointestinal disorder, infant, infantile colic, regurgitation

Functional gastrointestinal (GI) symptoms are frequently observed in infancy (1), whether they are accompaniments to physiological development or arise from maladaptive behavioural responses to internal or external stimuli (2). Various definitions and classification or diagnostic criteria for these disorders have been developed, including the Rome III criteria published in 2006 (1). Practical algorithms for managing many of these symptoms have also been published (3). The real frequency of these symptoms among young infants, however, remains uncertain (4), as do their consequences for future health. The aim here was to review published evidence and the opinion of practising clinicians on the prevalence and long-term health consequences of functional GI symptoms in infants of age <12 months.

METHODS

PubMed was searched from inception to November 2014 to find articles reporting the prevalence in population-based studies of infantile colic (including crying and fussing), regurgitation, functional constipation, functional diarrhoea, and dyschezia in infants younger than 12 months, as well as the longer-term effects on children's health. Intervention studies were not included.

A questionnaire was sent to general paediatricians, paediatric gastroenterologists, and other health care professionals involved with the care of infants and their families worldwide, asking them what criteria they used to diagnose the conditions under consideration, what they considered the local prevalence to be, and whether they had any unpublished local data. The questions for the survey were constructed by the lead author (Y.V.) and discussed with the coauthors. When consensus was reached, the questionnaire was distributed to practising clinicians via the authors, national societies of paediatrics and paediatric gastroenterology, and the "bulletin board" (a worldwide electronic communication tool for paediatric gastroenterologists) using the online SurveyMonkey tool. The total number of questionnaires distributed is unknown. Publications suggested by respondents were added to the literature search findings. Finally, a group of 15 international experts in the field met to discuss the data and to reach a consensus on the likely prevalence and longer-term consequences of these frequent GI symptoms, and to identify areas where more data are needed.

PREVALENCE OF FUNCTIONAL GI SYMPTOMS AT 0 TO 12 MONTHS

The characteristics and findings of studies reporting the prevalence of functional GI symptoms in infants age <12 months are summarised in supplemental Tables S1–S5 (*http://links.lww. com/MPG/A540*, *http://links.lww.com/MPG/A541*, *http://links.lww. com/MPG/A542*, *http://links.lww.com/MPG/A543*, and *http://links. lww.com/MPG/A544*). Figure 1 provides a visual representation of the findings, and Table 1 (5–9) summarises the prevalences from studies using Rome III criteria to define symptoms. Questionnaires were received from 369 respondents: 132 from the EU, 57 from Asia, 53 from Africa, 38 from North America, 28 from eastern Europe, 28 from the Middle East, 24 from South America, 4 from the Caribbean, 3 from Oceania, and 2 from Central America. Of these, 221 were paediatricians (other respondents included general physicians, nutritionists, and educators). Average estimated prevalences from the survey are indicated in Figure 1, and estimated prevalences by region are shown in supplemental Table S6 (*http:// links.lww.com/MPG/A545*).

Infantile Colic

Literature Search

Thirty studies were found, reporting a prevalence of infantile colic or crying/fussing problems of between 2% and 73% in infants younger than 12 months (4–6,10–36). Of these, 18 were prospective studies; the rest were cross-sectional or retrospective surveys (supplemental Table S1, *http://links.lww.com/MPG/A540*). Only 2 studies used the Rome III criteria of paroxysms of irritability, fussing, or crying that starts and stops without obvious cause, lasts ≥3 hours/day and occurs ≥3 days/week for ≥1 week, in infants
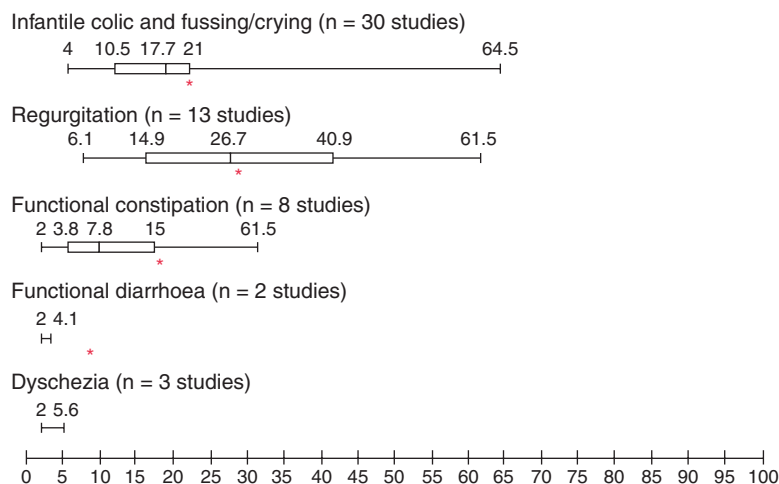

FIGURE 1. Estimated prevalence of functional gastrointestinal (GI) symptoms in infants younger than 12 months. Box shows 25th to 75th centile of literature values, with median marked; whiskers show full range. Study means were used wherein >1 value was reported. Asterisks show means from worldwide survey.

TABLE 1. Prevalence of all symptoms using Rome III criteria

Study, year (reference)	Country	Study design	No. in population (age range included in study, y)	Age group for symptom reported, mo	Prevalence, %
Infantile colic					
Chouraqui, 2011 (5)	France	Prospective population	1211 (1−4)	0−4	19
van Tilburg, 2015 (6)	USA	Cross-sectional survey	264 (0−3)	0−4	6
Regurgitation					
Chouraqui, 2011 (5)	France	Prospective population	1211 (1−4)	0−12	17.3
van Tilburg 2015 (6)	USA	Cross-sectional survey	264 (0−3)	0−12	26
Functional constipation					
Osatakul 2014 (8)	Thailand	Cross-sectional	1749	0−12	0.05
Turco 2014 (7)	Italy	Multicentre prospective cohort	465	3	12
				6	14
				12	11
van Tilburg 2015 (6)	USA	Cross-sectional survey	264 (0−3)	0−12	5
Functional diarrhoea					
van Tilburg 2015 (6)	USA	Cross-sectional survey	264 (0−3)	0−12	2
Dyschezia					
Chouraqui 2011 (5)	France	Prospective population	1211 (1−4)	0−6	5.6
Kramer 2014 (9)	Netherlands	Prospective cohort	1292	1	3.9
				3	0.9
van Tilburg 2015 (6)	USA	Cross-sectional survey	264 (0−3)	0−12	2

from birth to 4 months (Table 1). One of these was prospective and reported a prevalence of infantile colic of 19% (5), whereas the other was cross-sectional and reported a prevalence of 6% (6). Another 6 studies used the Wessel criteria (crying for ≥3 hours/day, for ≥3 days/week, for ≥3 weeks), reporting prevalences between 9% and 22% (16,19,26−29). The other studies used a variety of definitions. One study reported prevalences ranging from 9% to 16% depending on the definition used (19). The study reporting the highest prevalence was based on parental report of paroxysmal irritability (30). Studies including only infants aged younger than 4 months reported prevalences ranging from 4% to 28%.

A systematic review from 2001 of 15 community-based surveys of the occurrence of infantile colic found occurrence rates in the first 3 months of life ranging from 3% to 28% in prospective studies and from 8% to 40% in retrospective studies (37).

Worldwide Survey and Expert Consensus

The overall average worldwide prevalence of infantile colic reported by the survey respondents (n = 227) was 21%, with most respondents using the Rome III criteria and a few the Wessel criteria. The prevalence of ''colicky infants'' who may not meet formal diagnostic criteria was slightly higher, with a worldwide average of 24%.

The expert group noted that according to Rome III criteria, infantile colic occurs only before the age of 4 months. The consensus was that the worldwide prevalence of infantile colic is uncertain, but is estimated to be approximately 20%; good quality data are lacking.

Regurgitation

Literature Search

Thirteen studies reported a wide range of prevalences of regurgitation (from 3% to 87%) in infants younger than 12 months (4,11,6,38−46). Of these, 8 were prospective studies and 5 were cross-sectional. The criteria used to define regurgitation varied widely. Two studies used the Rome III criteria of 2 or more episodes per day for at least 3 weeks (Table 1), reporting prevalences of 17.3% and 26% (5,6). Other studies used definitions ranging from at least one episode per day to at least 4 episodes per day. In studies reporting on infants at different ages, prevalence was highest in the first few months of life and declined after approximately 6 months (supplemental Table S2, *http://links.lww.com/MPG/A541*).

Worldwide Survey and Expert Consensus

The respondents to the survey (n = 210) reported an overall average worldwide prevalence of regurgitation of 29%. Diagnosis is mainly symptom based, with some respondents using Rome III criteria or the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition/European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines. The overall prevalence of infants with more than 4 episodes of regurgitation per day was 23%.

The expert consensus was that the worldwide prevalence of infant regurgitation according to Rome III criteria is uncertain, but is estimated to be approximately 30%; good-quality data are lacking.

Functional Constipation

Literature Search

Eight studies were found, reporting prevalences of functional constipation ranging from 0.05% to 39.3% in infants younger than 12 months (4,6−9,11,45−49) (supplemental Table S3, *http://links.lww.com/MPG/A542*). Only 2 of the studies were prospective, 5 were cross-sectional and 1 was retrospective. Three of the studies used the Rome III criteria of passage of large diameter stools at intervals of less than twice per week, with retentive posturing and avoiding defecation by purposefully contracting the pelvic floor (Table 1). Of these, 1 prospective study found that functional constipation was present in 12% of the 465 infants at 3 months, 14% at 6 months, and 11% at 12 months after birth (7). The other 2 studies were cross-sectional and reported prevalences of 0.05% and 5% (6,8).

Worldwide Survey and Expert Consensus

The overall average worldwide prevalence of infant constipation reported by respondents (n = 198) was 18%. Approximately one-fifth of the respondents use the Rome III criteria, whereas the rest use specific symptoms such as frequency of defecation, consistency of stools, and pain experienced. The overall reported prevalence of constipation-like symptoms was 20%.

The expert consensus was that the worldwide prevalence of functional constipation in infants age younger than 12 months is uncertain, but is estimated to be approximately 15%, depending on the type of feeding; good quality data are lacking.

Functional Diarrhoea

Literature Search

The literature search found only 2 articles that specifically reported the prevalence of functional diarrhoea (4,6). An Italian prospective study reported a prevalence of diarrhoea (supplemental Table S4, *http://links.lww.com/MPG/A543*) of 4.1% at 0 to 12 months (4). In a US cross-sectional study, the prevalence of functional diarrhoea according to Rome III criteria (daily painless, recurrent passage of ≥3 large, unformed stools for ≥4 weeks starting after 6 months of age) was 2% among infants younger than 12 months (Table 1) (6).

Worldwide Survey and Expert Consensus

According to the respondents to the survey (n = 192), the overall average worldwide prevalence of functional diarrhoea (mainly diagnosed using Rome III criteria) was 9%.

The expert group noted that studies reporting the prevalence of functional, as distinct from acute, diarrhoea are scarce. They also noted that functional diarrhoea in children typically starts in the toddler age group and was often referred to in the past as ''toddlers' diarrhoea''; a diagnosis below the age of 2 years is not frequent. The consensus was that the worldwide prevalence of functional diarrhoea is unknown, because good quality data are missing.

Dyschezia

Literature Search

Only 3 studies reporting the prevalence of infant dyschezia were found (5,6,9) (supplemental Table S5, *http://links.lww.com/MPG/A544*). All 3 used the Rome III criteria of at least 10 minutes of straining and crying before successful passage of soft stools without other health problems in an infant younger than 6 months of age (Table 1). In a recent US cross-sectional study, the prevalence of dyschezia according to Rome III criteria was 2% among infants younger than 12 months (6). A French prospective study found a prevalence of 5.6% at 0 to 6 months (5). A recent prospective cohort study of 1292 infants in the Netherlands found that 3.9% fulfilled the Rome III criteria for dyschezia at 1 month and 0.9% at 3 months; however, parents of 17.3% and 6.5% of infants reported symptoms preceding defecation while not strictly fulfilling the Rome III criteria at these time points (9).

Worldwide Survey and Expert Consensus

Of the respondents to the survey (n = 205), 69% were aware of infant dyschezia; 36% classified it as part of the colic spectrum, and 44% classified it as functional constipation. The expert consensus was that infant dyschezia appears to be not well known and seems to be often classified as colic or constipation, which

will therefore have an impact on the management. It appears that there is a possibility to improve the definition of this entity. Therefore, more awareness and education around the condition is required.

FUTURE HEALTH OUTCOMES OF FUNCTIONAL GI SYMPTOMS

Literature Search

Literature on the future health impact of functional GI symptoms before 12 months of age is scarce. A number of studies have looked at the longer-term impact of infantile colic, but few have looked at the other symptoms discussed in this article.

Infantile Colic

For infantile colic, associations with later GI problems, atopy, migraine, and behavioural/cognitive problems have been studied. One prospective study (n = 75) found that 28% of infants with colic developed functional GI problems by the age of 13 years, compared with 6% without (50). Another prospective study (n = 96) reported an association between colic at age 31 to 87 days and recurrent abdominal pain and allergic disorders in the next 10 years (51). One prospective study (n = 90) found no association between infantile colic and subsequent risk of developing asthma and/or atopy (22), whereas another (n = 116) found an association in high-risk infants (≥1 atopic relative) (52). A retrospective case-control study found that children and adolescents ages 6 to 18 years with migraine (n = 208) were more likely (odds ratio 6.61, 95% confidence interval [CI] 4.38–10.00) to have experienced infantile colic than controls (n = 471) (53). A prospective study found that infants with colic at 3 months (n = 338) had more sleeping problems and more frequent temper tantrums at 3 years than did those without colic (n = 866) (54). A survey of parents of 228 toddlers who had had infantile colic showed that those who had received chiropractic treatment were twice as likely not to experience long-term sequelae such as temper tantrums and frequent nocturnal waking (55). A comparison of 40 children ages 6 to 8 years found that those who had had infantile colic had maternal ratings suggestive of more difficulty with emotional regulation and displayed a more impulsive cognitive style (56), and another reported that ex-colicky 4-year-old children (n = 52) displayed more negative emotions than controls (n = 118) according to the temperament scale (mean score (1–5) 3.38 vs 2.88, P = 0.001) and had more reported stomach aches (57). A prospective study (n = 202) recently reported that the duration and frequency of crying bouts in infancy was correlated with Child Behavior Check List scores at 4 years (58).

Follow-up of a cohort of 75 school-age children who had been hospitalised for persistent crying in infancy found a significantly higher prevalence of mental health problems and mental disorders compared with community controls (26% vs 10%, risk ratio 2.56, 95% CI 1.72–3.80) (59), but another prospective study looking at children ages 2 to 4 years who had cried excessively at 6 to 8 weeks reported little impact on the children's later behavioural development (60). A prospective study in 117 very-low-birth-weight infants found that longer duration of fussing and crying in extremely early infancy (0–6 weeks), but not at 5 months, was associated with less optimal psychomotor development at 24 months (61). A prospective cohort study of 561 children found that those with prolonged crying at 6 to 13 weeks had lower intelligence quotient scores at 5 years than the control group (62). Another study found that children (n = 53) referred for persistent crying in infancy (mean 3.8 months) were at increased risk for hyperactivity problems and academic difficulties later in

childhood (8–10 years) compared with classroom controls (n = 64) (63).

A meta-analysis of 22 longitudinal studies found that children with previous regulatory problems of feeding/sleeping/crying had more behavioural problems than controls (weighted mean effect size 0.41, 95% CI 0.28–0.54) (64). Studies have reported that regulatory problems in the first year of life are associated with hyperkinetic symptoms throughout childhood (65), infections and behavioural problems at the age of 2 years (66), behavioural problems at 3.5 years (67), as well as deficits in preschool adaptive behaviour and social skills, and eating problems at 20 and 56 months (68). One study found that regulatory problems at 5 months in girls were directly predictive of lower cognition at 56 months, whereas in boys the influence on cognition at 56 months was mediated by delayed mental development at 20 months (69). The UK Avon Longitudinal Study of Parents and Children found that having multiple regulatory problems was strongly associated with dysregulated behaviours later in childhood (70).

Regurgitation

In an Australian prospective birth cohort (41), infants with spitting on 90 days or more during the first 2 years of life were more likely to have gastro-oesophageal reflux symptoms at 9 years of age (relative risk 2.3, 95% CI 1.3–4.0 vs those with no spitting). Another study of infants with gastro-oesophageal reflux diagnosed before age 11 months found that 70% were still affected after 1 year of conservative treatment; of the 28 children followed up in the longer term, pathological reflux persisted in 7 of them at age 4, 5 at age 5, and 3 beyond 5 years (71).

Functional Constipation

A follow-up study of 47 children who had functional constipation in the first year of life and were seen in a tertiary centre, 69% of whom had recovered after 6 months, found that a relapse had occurred in 15% within 3 years. A duration of <3 months before referral was significantly correlated with a better outcome, suggesting that early therapeutic intervention may beneficially contribute to the resolution of constipation (72). Another study reported long-term outcomes in 90 children with chronic constipation before the age of 4 years. Follow-up a mean of 6.9 years after initial evaluation found that 57 (63%) had recovered; the recovery rate was higher in those ages younger than 2 years at initial evaluation (73). A few studies have reported a history of GI symptoms in children with autistic spectrum disorder (74–76), whereas others have found no such association (77,78).

Expert Consensus

The experts noted that infantile colic (by definition) does not start after 4 months of age (and in most cases it has disappeared by 4 months), so only associations with other conditions (and not future occurrence of colic) are relevant. The consensus was that infantile colic may be associated with future health problems, as suggested by the available literature; however, the possibility that these health problems present initially as infantile colic cannot be ruled out. Prospective studies are required to confirm establish these relationships, although proving causality would be impossible.

Regarding regurgitation, the experts noted that failure to treat reflux disease properly has consequences, but it is not known whether this is also the case for infant regurgitation; however, it was felt that inappropriate management may have adverse effects. The consensus was that it is uncertain if infant regurgitation is

associated with future health problems; there are associations occurring within the literature, but prospective studies are required to confirm this hypothesis.

The experts noted that while infantile colic and regurgitation will usually resolve without management, this is less likely for constipation. The consensus was that functional constipation in infants may be associated with future GI problems, but this is uncertain and prospective studies would be needed to confirm it; one study suggests a positive impact of early treatment.

For functional diarrhoea, the expert consensus was that functional diarrhoea before the age of 12 months appears to have no long-term consequences. As regard dyschezia, the consensus was that there is no evidence that infant dyschezia leads to later functional constipation or other GI symptoms.

DISCUSSION

Studies on the prevalence and long-term health outcomes of functional GI symptoms other than colic in infants younger than 12 months are scarce. For most of the symptoms, many of the prevalence studies were conducted several decades ago; the study designs, populations studied and definitions used make it difficult to compare studies and draw firm conclusions. The reported prevalences varied widely: from 2% to 73% (30 studies) for infantile colic, 3% to 87% (12 studies) for infant regurgitation, and 0.1% to 39% (8 studies) for functional constipation; few studies used the Rome III criteria for these symptoms (Table 1). The small number of studies found for functional diarrhoea and dyschezia reported prevalences <10%.

The findings from the survey among practising clinicians are largely consistent with the average incidence found in the literature. Interestingly, infantile colic and functional diarrhoea were the functional GI disorders that were according to the respondents mainly diagnosed by Rome III criteria. Constipation was diagnosed according to Rome III criteria by only approximately 20% of the respondents, and the biggest gap in usage of standardised diagnosis was for dyschezia, which was not perceived by approximately 80% of the respondents as a separate diagnostic entity. Examination of any regional differences revealed by the survey responses, and comparison with published regional data, may be considered as the next step in this project.

On the basis of the evidence available, the experts considered that the likely worldwide prevalences according to Rome III criteria are approximately 20% for infantile colic, 30% for regurgitation, and 15% for functional constipation. The limited data for functional diarrhoea and dyschezia suggest prevalences <10%, but the latter in particular is not well understood. In the future, collection of reliable data on all these symptoms according to agreed criteria is required, to obtain a more accurate estimate. Infantile colic appears to be associated with future health problems such as GI disorders, migraine, and behavioural/developmental problems. Evidence for future problems associated with the other symptoms is lacking, but it seems that early management of constipation may be important.

Although this review has considered several functional GI symptoms separately in terms of prevalence and future health outcomes, there is overlap between the various symptoms in practice. For example, a recent study looking at the effects of a novel infant formula found that colic at 4 weeks of age was associated with flatulence, abdominal distension, constipation, diarrhoea, and regurgitation (79). In a survey about functional GI disorders performed among 273 paediatricians (80), 2747 infants ages between 0 and 6 months (mean age 6.9 weeks, exclusively formula fed) were studied. Only a single functional GI symptom was present in 602 infants (regurgitation in 63.8%, colic in 20.5%, constipation in 9.1%), but several symptoms were combined in

2145 infants. The most frequent associations seen in the infants were bloating and colic (36.2%), regurgitation and colic (22.4%), and bloating with regurgitation (9.7%). As assessed with a French quality of life scale (QUALIN), the infants were more uncomfortable when at least 2 symptoms were combined than when there was a single symptom (5.9 vs 6.5, $P < 0.001$) (80).

Another factor that needs to be taken into account is feeding—whether an infant is breast-fed or formula-fed, and which type of formula is used, will influence the development of functional GI symptoms. For example, a study in the Netherlands found that breast-fed infants had more frequent, softer stools in the first 3 months of life than did infants fed standard formula (81). Average daily defecation frequency decreased significantly during the first 3 months (from 3.65 to 1.88 times/day), whereas no significant changes were observed in infants fed standard formula or mixed feeding. Many of the studies discussed here date from before the introduction of infant formulas containing prebiotic and probiotic agents. New ingredients introduced in the past 10 years may have had an impact on the prevalence and outcome of some of the symptoms discussed. In colicky infants, trying a nonallergic diet for a short time followed by a challenge has been shown to be of benefit in some studies (82).

In conclusion, the functional GI symptoms considered here appear to occur in a significant proportion of infants younger than 12 months old (possibly up to 30%) and may have an impact on future health outcomes. Collection of reliable data in prospective studies and according to agreed criteria is needed to obtain more accurate estimates of the prevalence and consequences of these common symptoms.

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