Quality of Life of Infants with Functional Gastrointestinal Disorders: A Large Prospective Observational Study

Camille Jung[1], Laurence Beck[2,*], Thierry Hanh[2] and Marc Bellaiche[3]

[1]*Clinical Research Center, Créteil Intercommunal Hospital Center, 40 avenue de Verdun; 94000 Créteil, France*

[2]*Nestlé France, 7 boulevard Pierre Carle, BP 900 Noisiel, 77446 Marne-la-Vallée Cedex, France*

[3]*Department of Pediatric Gastroenterology and Nutrition, Robert Debré University Hospital, APHP, 48 boulevard Sérurier, 75019 Paris, France*

Abstract: *Background*: Functional gastrointestinal disorders (FGID) are very common during infancy, leading to frequent medical consultations. The aim of this large, prospective study was to assess the quality of life (QoL) and clinical management of infants with FGID.

Methods: Completely or partially bottle-fed infants under 5 months old, presenting one or more FGID (regurgitation, constipation, diarrhea, crying/fussing), were enrolled during initial consultation by 111 pediatricians in private practice throughout France and reassessed at one month. Parents were asked to complete the QUALIN QoL questionnaire at inclusion and at Day 15.

Results: A total of 815 infants (mean age 2.1±1.2 months) were evaluable. Mean QoL score improved from +27.2±15.1 at inclusion to +38.0±12.9 at day 15 (p<0.0001) irrespective of FGID symptoms. Multivariate analysis indicated that younger age, dietary advice, and partial breastfeeding were associated with better QoL outcome. Gastrointestinal symptoms showed significant regression at Day 30. The number of bottle feeds followed by external reflux episodes decreased from 80.0±27.4% to 36.1±31.4% at Day 30 (p<0.0001), the weekly number of stools increasing from 3.9±4.0 to 8.0±3.7 (p<0.0001).

Conclusion: Medical management based on information, reassurance, lifestyle advice and dietary intervention improved QoL in infants with FGID and led to a reduction in FGID symptoms.

Keywords: functional gastrointestinal disorder, infant, quality of life, QUALIN, nutrition.

BACKGROUND

Functional gastrointestinal disorders (FGID) are very frequent during the first months of life and pediatricians are often confronted with infants suffering from their symptoms. The results of a large, prospective, population-based study indicated that approximately 55% of infants under 6 months old suffer from FGID, 39% of these infants experiencing a combination of gastrointestinal (GI) symptoms [1]. A recent review of studies reporting the prevalence of different FGID in infants from birth to 12 months, completed by a survey of experts, concluded that the most widespread forms are regurgitation, with a likely worldwide prevalence of about 30%, followed by infantile colic (20%) and constipation (15%) [2]. These symptoms are considered to be physiological or to reflect adaptation of the digestive system to nutrients. Although FGID have no underlying organic cause and are not life-threatening, they nevertheless impair quality of life and are stressful for infants and parents alike.

The negative impact of FGID on quality of life has been highlighted in many studies in both adults [3,4] and children [5]. In a study of 123 children aged 2 to 3 years old, quality of life assessed using the PedsQL4.0 Generic Core Scale was found to be significantly impaired in toddlers presenting FGID compared to those without FGID [6]. However, few data are available for infants less than one year old.

One of the few tools available for evaluating quality of life in infants is the QUALIN questionnaire, which was specially developed for use in infants and toddlers. This questionnaire is available in various languages and has been validated in several European countries [7]. It has already been used to assess quality of life in children with GI or nutritional symptoms [8,9].

The aim of this prospective study conducted in France was to evaluate the quality of life of infants under 5 months of age suffering from FGID, using the French version of the QUALIN questionnaire, as well as their clinical management and the efficacy of treatment with regard to quality of life and clinical symptomatology.

*Address correspondence to this author at the Medical Department, Nestlé France, BP 900 Noisiel, 77446 MARNE-LA-VALLEE Cedex, France; Tel: +33 1 60 53 14 93; Fax: +33 1 60 53 14 57; E-mail: Laurence.beck@fr.nestle.com

METHODS

Subjects

Infants aged from 0 to 5 months fed at least partially on infant formula and brought for initial consultation for FGID were eligible for inclusion in this prospective, observational study. Between May 12th 2014 and April 1st 2015, pediatricians in private practice throughout France were invited to consecutively enroll 10 infants meeting these inclusion criteria. Allergic and exclusively breastfed infants were not eligible for inclusion. As this prospective study had no impact on everyday clinical practice, no ethical review board approval was requested. However, the study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki, as well as local regulations, in particular regarding data protection. The parents of all infants included gave their oral agreement to their child's participation in the study.

Demographic and Medical Data

Demographic and medical data were entered by the pediatrician on an electronic case report form at inclusion. Baseline demographic data included birth term, weight and height at birth and at inclusion, and sex. The medical data recorded comprised type of feeding (exclusively bottle feeding or mixed, early weaning), type of infant formula fed, and presence of the following symptoms: constipation, diarrhea, regurgitation, and persistent crying. To score the intensity and frequency of GI symptoms, parents were asked to indicate stool frequency during the previous week and the number of regurgitations during the previous 24 hours and also to score the intensity and frequency of regurgitations on a scale of 0 to 10. Clinical management strategies, including change of infant formula, medicine prescription, and provision of medical advice were also recorded.

One month after inclusion, a Day 30 medical chart was completed by the pediatrician at a follow-up medical consultation. Data concerning the course of FGID, as well as the efficacy and tolerance of the prescribed infant formula and medication, were recorded.

Quality of Life

Infant quality of life (QoL) was assessed using the validated French version of the QUALIN questionnaire [7], completed by the parents at inclusion and 15 days after inclusion either at home or in the pediatrician's office. The questionnaire includes 34 items with 6 possible answers, scored from -2 (quite false) to +2 (entirely true). Thus, the overall score ranges from -68 (poor QoL) to +68 (excellent QoL). Four topics are addressed: behavior and communication, ability to remain alone, family environment, and psychological and somatic well-being.

Statistical Analysis

Proportions were described as percentages and continuous variables by the mean and standard deviation. Qualitative variables were compared using the Chi-square test. Means were compared using ANOVA, Student's t-test or the paired Student's t-test for paired data. The primary endpoint was assessed by comparing the QUALIN scores determined at day 0 and day 15 using the paired Student's t-test. The two-sided alpha level of significance was set at 5%. A stepwise multivariate analysis was performed to identify factors associated with an increase in the QUALIN score. This took into account all factors with $p<0.1$ in the univariate analyses. Odds ratios (OR) with the corresponding Wald confidence interval (CI) were calculated in multivariate analyses. Analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

A total of 1122 infants aged from 0 to 5 months were consecutively recruited by 111 pediatricians in private practice. For the statistical analysis, we excluded 307 subjects who did not meet the inclusion criteria (41 cases), who did not present symptoms of FGID (32 cases), who failed to respect the interval between the two scheduled medical visits (2 cases), or for whom the two questionnaires were not completed (232 cases). Finally, 815 subjects (mean age [± SD] = 2.1 ± 1.2 months) were retained for analysis. Demographic and medical data at inclusion are reported in Table **1**. Overall, regurgitation, whether isolated or associated with other symptoms (constipation or diarrhea), was the most common functional symptom (n=629, 74%) followed by constipation, with or without regurgitation (n=255, 30%). Colic, as expressed by constant crying, was observed in only 28 infants (3.4%).

Quality of Life

At inclusion, the mean total QUALIN score was 27.2 (±15.1), increasing to 38.0 (±12.9) at Day 15

Table 1:   Demographic and Medical Data at Inclusion

	N (%)	Mean±SD
Male Female	426 (52.2) 387(47.4)	
Age (months)		2.1±1.2
Weight at birth (kg)		3.25±0.45
Weight at inclusion (kg)		4.9±1.14
Feeding		
Exclusively infant formula fed	569 (70.2)	
Partially breastfed	242 (29.8)	
Early weaning	33 (4.2)	
Functional Gastrointestinal Disorder		
Regurgitation	438 (53.7)	
Regurgitation and constipation	134 (16.4)	
Constipation	122 (14.8)	
Regurgitation and diarrhea	57 (6.9)	
Constant crying	28 (3.4)	
Diarrhea	24 (2.8)	

($p<0.0001$). Significant improvements from baseline to Day 15 were also seen in all four QUALIN subcategories considered individually: "behavior and communication", "psychological and somatic well-being", "ability to remain alone", and "family environment" (mean differences in score: 3.82±5.35 [$p<0.0001$], 3.36±4.89 [$p<0.0001$], 0.36±2.06 [$p<0.0001$] and 0.47±1.63 [$p<0.0001$], respectively). Irrespective of the specific FGID symptoms presented by the infants, overall QUALIN score and scores for the subcategories "behavior/communication" and psychological and somatic well-being" increased to a statistically significant extent from baseline to Day 15 (Table **2**). In contrast, no significant difference between the baseline and Day 15 scores for the QUALIN subcategories "ability to remain alone" and "family environment" was seen in any of the individual FGID symptom groups. The changes in overall and subcategory QUALIN scores between baseline and Day 15 did not differ significantly according to the type of FGID symptoms presented by the infants.

Increase in QUALIN score was associated with improvement in FGID (mean increase +11.60±11.42 in infants showing improvement versus +8.21±11.57 in those showing no improvement, $p=0.001$) and with the provision of dietary advice by the physician (mean increase +12.4±3.82 versus +9.81±6.55, $p=0.009$). In contrast, the change in QUALIN scores from baseline to day 15 did not differ significantly between infants who were partially breastfed and those nourished exclusively with infant formula, between those weaned early and those not weaned early, or between those receiving and not receiving a prescription for a medicine. Multivariate analysis showed that QUALIN scores were more likely to improve in younger infants, those who were partially breastfed, and those whose parents received dietary advice (Table **3**).

Management of the GI Symptoms

Most pediatricians prescribed an infant formula (IF) targeting the functional GI symptoms. In this study,

Table 2: Mean Changein QUALIN Scores between Inclusion and Day 15 According to Type of Functional Gastrointestinal Disorder (FGID[a])

QUALIN score	Mean change in score from inclusion to D15 (mean ± SD) by type of FGID					
	Constipation (N=122)	Diarrhea (N=24)	Regurgitation (N=443)	Constant crying (N=35)	Regurgitation and diarrhea (N=57)	Regurgitation and constipation (N=134)
Total score	+11.46±30.17 ($p<0.0001$)	+6.77±16.44 ($p=0.0438$)	+11.02±53.84 ($p<0.0001$)	+10.60±18.48 ($p=0.0007$)	+7.21±22.01 ($p=0.0136$)	+9.99±31.37 ($p=0.0002$)
Behavior/communication	+4.23±12.65 ($p=0.0002$)	+2.47±6.89 (NS)	+3.54±22.57 ($p=0.0010$)	+3.87±7.75 ($p=0.0032$)	+2.21±9.23 (NS)	+3.23±13.15 ($p=0.0046$)
Ability to remain alone	-0.22±5.74 (NS)	-0.90±3.13 (NS)	-0.16±10.24 (NS)	-0.60±3.52 (NS)	-0.04±4.19 (NS)	-0.12±5.97 (NS)
Family environment	0.02±4.40 (NS)	-0.13±2.40 (NS)	+0.13±7.86 (NS)	+0.23±2.70 (NS)	-0.03±3.21 (NS)	+0.18±4.58 (NS)
Psychological and somatic well-being	+4.71±12.33 ($p<0.0001$)	+3.74±6.72 ($p=0.0065$)	+4.72±22 ($p<0.0001$)	+4.25±7.55 ($p=0.0009$)	+2.98±8.99 ($p=0.0125$)	+4.29±12.82 ($p=0.0001$)

[a]FGID: functional gastrointestinal disorder; SD: standard deviation.

Table 3: Multivariate Analysis of Factors Associated with an Increase in Quality of Life

Variable	Change in QoL[a]	Reference	p-value	Odds ratio	95% CI	
Age <1month vs >3 months	Increase	Stability	0.0470	1.71	1.01	2.89
Age [1;2[months vs >3 months	Increase	Stability	<0.0001	2.42	1.63	3.61
Age [2;3] months vs >3 months	Increase	Stability	0.0299	1.56	1.04	2.34
Partial breastfeeding Yes vs. No	Increase	Stability	0.0241	1.43	1.05	1.94
Dietary advice Yes vs. No	Increase	Stability	0.0016	1.63	1.20	2.19

[a]QoL: quality of life (assessed using the QUALIN questionnaire).

almost all the prescribed IF contained probiotics (*Lactobacillus reuteri*). About 52% of pediatricians recommended an anti-reflux IF thickened with starch up to 2g/100mL and 42% a low-lactose content formula. Thirty-five percent of the prescribed IF contained partially hydrolyzed proteins and 35% were acidified formulas. For infants presenting regurgitation as the sole symptom of FGID, anti-reflux IF was the most widely prescribed formula, representing 77% of IF prescriptions, while an acidified formula with a low lactose level and containing probiotics was the formula of choice for infants with constipation, constituting 79% of IF prescriptions. Pediatricians recommended a low-lactose, probiotic-containing formula for 30% of infants presenting diarrhea and for 56% of those presenting infant colic.

Mean body weight at day 30 was 5.77 kg (±1.09) corresponding to a mean weight gain of 0.36 kg (±1.09) compared to baseline. In most (95%) cases, the formula prescribed was well tolerated. Its efficacy was considered as quite good in 9% of cases, good in 39% of cases and excellent in 45% of cases. Use of the prescribed infant formula was continued beyond Day 30 in 89% of cases.

Medical prescriptions were frequent and concerned 25% (n=210) of the infants included, varying from 16% in the group of infants presenting constipation to 34% in the regurgitation/diarrhea group. Among the infants for whom a medicine was prescribed, 32% were prescribed an alginate agent, 19% simeticone, 12% trimebutine and 14% a proton pump inhibitor (PPI). Overall, 16% of infants presenting regurgitation received treatment with an antacid or a PPI.

Prescriptions for plant extract solutions represented 8% of total prescriptions, probiotics accounting for a similar percentage. Probiotics and dietary supplements were essentially prescribed for infants who were constantly crying or for those with diarrhea (for 14% and 12% of infants with these symptoms, respectively).

In 286 cases (34%), the pediatricians gave dietary and lifestyle advice. An anti-Trendelenburg sleeping position was counseled in 44% of these cases and abdominal massages in 16%. Dietary advice comprised principally changing the water used for the preparation of the infant formula (16%) for water richer in magnesium, and changing the rhythm or duration of bottle feeding or the quantity of bottles used, or early weaning (11%). In four cases, pediatricians gave tips on how best to carry the infants and in two cases osteopathy and reflexology were proposed to the family.

Course of FGID

At the clinical reassessment at one month, the clinical condition of the infants was seen to be improved in most cases. In the regurgitation group, the frequency of bottle feeds followed by regurgitation decreased from 73% at inclusion to 35% at day 30 (p<0.0001), the score attributed to the intensity of regurgitation scored on a scale of 0 to 10 decreasing from 4.53±4.95 to 1.81±1.74 (p<0.0001). Overall, 84% of infants with regurgitation were considered to be better at one month. Improvement was seen in 93% of the infants with constipation, 81% showing improvement within the week following the first medical consultation. The decrease in regurgitation was associated with an increase in the number of stools passed per week, from 3.89±4.00 to 7.96±3.68 (p<0.0001). Infants with frequent crying/fussing were less symptomatic at one month in 88% of cases. Infants with diarrhea passed fewer stools per week (a

mean of 9.41±3.33 compared to14.25±6.81at baseline; p<0.0001) and diarrhea stopped altogether in 54% of cases.

DISCUSSION

This large prospective observational study, implicating 111 pediatricians, followed up for 30 days 815 infants (mean age 2.1±1.2) presenting FGID. To the best of our knowledge, this is the first study to report impaired QoL in this population and improvement in QoL after medical care.

GI symptoms are among those most frequently encountered in pediatrics [1, 2]. As reported in previous studies, regurgitation was the most common symptom (present in 74% of the infants included) followed by constipation (30%), diarrhea (9%) and constant crying (3.4%), these symptoms occurring in combination in 22.5% of cases. The parents of infants with FGID frequently seek help to relieve their children's distress, requesting information and solutions to improve their wellbeing. The mean QoL score of the infants assessed, calculated from parent responses to the QUALIN questionnaire was +27±15 at inclusion on a scale from -68 to +68. At 15 days after the initial consultation, the mean QoL score showed substantial improvement, reaching +38±13 (p<0.0001), emphasizing the positive impact of early medical management in infants with FGID. As we had no data on the QoL of infants with no FGID, we could not compare the QoL of infants with FGID and that of healthy control infants. In a previous study, using the PedsQL4.0 Generic Core Scale to measure QoL, the mean QoL score of infants not suffering from FGID was 10 points higher on a scale of 100 than that of infants with FGID (p<0.001) [6]. Similar impairment of QoL by 10 points on a 100 scale (p<0.05) was also reported in a study in older children with FGID compared to healthy children [5]. As FGID are not life-threatening conditions, improvement in QoL is the principal target of clinical care and should be assessed by the pediatrician.

Use of a QoL questionnaire could be a useful tool for the medical management of infants with FGID [6]. As expected, an association was found between an increase of the Qol Score and an improvement in FGID. Although the QUALIN questionnaire was not specifically developed for infants under 3 months of age [7], it was used in a study in neonates with respiratory infections [10] and no difficulties in its completion were reported. However, the questions concerning "ability to remain alone" might not be well suited to very young infants, and this might explain the lower scores attributed for this subcategory in our study.

Whatever the type of FGID presented by the infants, medical management was mainly based on dietary advice (prescription of an appropriate IF, lifestyle advice) and reassurance. Regurgitation is physiological in infants and should be distinguished from gastroesophageal reflux disease (GERD) which may lead to complications [11]. Recommended treatment combines reassurance of the parents, explanations about regurgitation, and advice concerning the quantity and frequency of bottle feeds. In this study, pediatricians reported having given dietary and lifestyle advice in 34% of cases and the mean overall QUALIN score was significantly higher in the group of infants whose parents had received such advice compared to the group whose parents had not received such advice. This observation confirmed the importance of informing, supporting and reassuring parents. Surprisingly, the pediatricians counseled the anti-Trendelenburg sleeping position for about 15% of the infants evaluated, although its efficacy is not proven and is not recommended [12, 11]. Thickened and anti-regurgitation IF have long been proposed to combat regurgitation, as these formulas can decrease the amount of visible regurgitation by reducing their volume and frequency, and can also improve sleep [13, 14]. Use of a thickened diet for healthy infants with substantial regurgitations is therefore recommended [11]. In our study, 77% of the infants presenting regurgitation were prescribed a thickened formula, suggesting that the use of these IF is widespread. Improvement was noted in 91% of infants who received a thickened diet and the IF was well tolerated by 94% of the recipients. It is also noteworthy that 46% of infants suffering from regurgitations were prescribed a partially hydrolyzed whey protein formula. A recent double-blind, comparative study indicated a positive impact on regurgitation frequency of a thickened formula including partially hydrolyzed protein compared to a non-hydrolyzed thickened formula [15]. This positive impact might be linked to a potentially faster rate of gastric emptying in the presence of hydrolyzed protein compared to intact protein. A randomized crossover study in 28 infants under 1 year of age suffering from gastroesophageal reflux showed a significantly higher percentage of gastric emptying after 60 minutes in infants fed a whey-hydrolysate formula compared to those receiving a casein–predominant

formula [16]. Another study in 201 infants with or without GERD showed no difference in the percentage of residual gastric activity at 120 minutes between infants fed breast milk (n=23), a hypoallergenic (HA) formula (n=20) or a whey formula (n=55), whereas in infants fed a casein-predominant formula (n=55), a significantly higher residual gastric activity was observed [17]. As yet, there are not enough data on which to base a specific recommendation on the quality and hydrolysis of protein likely to benefit children with regurgitation [18].

With regard to pharmacologic therapies, the prescription of antisecretory agents, gastroprotective agents such as alginates or simeticone, or prokinetic agents is not recommended [11, 19, 20]. Nevertheless, 16% of infants with regurgitation included in our study were prescribed an antiacid or PPI, highlighting the difficulties faced by pediatricians in proposing an appropriate treatment to the parents of such children, who sometimes specifically request prescription of a medicine.

For infants with constipation, once an organic cause has been ruled out, reassurance and close follow-up are sufficient. There is no evidence to support the use of magnesium-rich mineral water intake. On the contrary, there is a risk of exceeding the recommended mineral intake if solely mineral-rich water is used [21]. In our study, reflecting current practice, pediatricians frequently (in 16% of cases) recommended the use of highly mineralized water for some of the day's bottles. The use of an infant formula containing prebiotics to accelerate transit is considered to be safe and may be effective [22]. In our observational study, prebiotics were not prescribed. However, 88% of infants with constipation were prescribed an IF containing a probiotic (*L. reuteri*), which was considered to be effective and well tolerated. These subjective data were confirmed by the increased weekly stool frequency at one month (7.8 vs. 3.9 at inclusion; p<0.0001). A previous randomized, placebo-controlled study similar showed a significantly higher frequency of bowel movements at 2, 4 and 8 weeks in infants with FGID fed an IF supplemented with *L. reuteri* (DSM 17938) [23]. However, at present there are insufficient data to recommend the use of prebiotics or probiotics for this condition [22, 24].

In published studies, the prevalence of infant colic under 12 months of age varied from 2 to 73% [25], depending greatly on the definition of colic. One study reported a prevalence ranging from 9 to 16% according to the definition used [26]. In a prospective study including 2879 infants, 37% of the children with FGID suffered from colic [1]. In our study, the frequency of infant colic was much lower (3.4%). However, the physicians participating in our study were requested to report persistent and continuous crying in the infants included as a measure of colic. The frequency of infant colic could therefore have been under-estimated in light of the Rome III or Wessel criteria [27]. As expected, the symptoms of infant colic generally showed regression at one month. The results of several studies have suggested a role of the gut microbiotia in the physiopathology of infant colic [28]. The efficacy of the probiotic *L reuteri* in reducing the duration of crying and fussing has been shown in various randomized control trials and its use, notably that of the DSM 17938 strain, could constitute an effective treatment for infant colic [29, 30, 31]. A recent meta-analysis of the efficacy of *L. reuteri* DSM 17938 acknowledged its impact on crying time in infants with colic [32].

CONCLUSIONS

FGID are frequent in infancy and impair QoL. The clinical management of these functional disorders is based on information, reassurance, lifestyle advice and dietary intervention. In this large observational study, clinical management was effective in both reducing symptoms and improving QoL, the main objective of treatment for FGID. Objective data confirmed the clinical impressions of the pediatricians. Interestingly, it appears that clinical practices frequently differ from evidence-based recommendations. Notably, measures such as adoption of the anti-Trendelenburg sleeping position are still widely advocated without any proof of efficacy, and the prescription of medicines such as prokinetics or PPI is frequent even though their use is not recommended for this kind of disorder. Good practical information sheets could be useful to inform practitioners and parents about the effectiveness of medical counseling and reassurance and on the potential side-effects of certain medicines in infants with FIGD.

ACKNOWLEDGEMENTS

ABBREVIATIONS

FGID   = Functional gastrointestinal disorder

GERD   = Gastroesophageal reflux disease

GI   = Gastrointestinal

HA formula = Hypoallergenic formula

IF   = Infant formula

OR   = Odds ratio

PPI   = Protein pump inhibitor

QoL   = Quality of life

QUALIN   = Infant Quality of Life questionnaire

REFERENCES

[1]   Iacono G, Merolla R, D'Amico D, *et al*. The Pediatric Study Group on Gastrointestinal Symptoms in Infancy. Gastrointestinal symptoms in infancy: a population-based prospective study. Dig Liver Dis 2005; 37: 432-8.
https://doi.org/10.1016/j.dld.2005.01.009

[2]   Vandenplas Y, Abkari A, Bellaiche M, *et al*. Prevalence and health outcomes of functional gastrointestinal symptoms in infants from birth to 12 months of age. J Pediatr Gastroenterol Nutr 2015; 61: 531-7.
https://doi.org/10.1097/MPG.0000000000000949

[3]   Aro P, Talley NJ, Agréus L, *et al*. Functional dyspepsia impairs quality of life in the adult population. Aliment Pharmacol Ther 2011; 33: 1215-24.
https://doi.org/10.1111/j.1365-2036.2011.04640.x

[4]   Kaji M, Fujiwara Y, Shiba M, *et al*. Prevalence of overlaps between GERD, FD and IBS and impact on health-related quality of life. J Gastroenterol Hepatol 2010; 25: 1151-6.
https://doi.org/10.1111/j.1440-1746.2010.06249.x

[5]   Youssef NN, Murphy TG, Langseder AL, Rosh JR. Quality of life for children with functional abdominal pain: a comparison study of patients' and parents' perceptions. Pediatrics 2006; 117: 54-9.
https://doi.org/10.1542/peds.2005-0114

[6]   Van Tilburg MA, Hyman PE, Walker L, *et al*. Prevalence of functional gastrointestinal disorders in infants and toddlers. J Pediatr 2015; 166: 684-9.
https://doi.org/10.1016/j.jpeds.2014.11.039

[7]   Manificat S, Dazord A, Langue J, *et al*. Evaluation of the quality of life of infants and very young children: validation of a questionnaire. Multicenter European study. Arch Pediatr 2000; 7: 605-14. French.

[8]   André E, Hodgkinson I, Bérard C, des Portes V. Quality of life of very disabled children: a questionnaire about the role of health status and tube feeding. Arch Pediatr 2007; 14: 1076-83. French.

[9]   Holenweg-Gross C, Newman CJ, Faouzi M, Poirot-Hodgkinson I, Bérard C, Roulet-Perez E. Under nutrition in children with profound intellectual and multiple disabilities (PIMD): its prevalence and influence on quality of life. Child Care Health Dev 2014; 40: 525-32.
https://doi.org/10.1111/cch.12085

[10]   Méndez Rubio I, Lázaro de Mercado P, Carbonell Estrany X, Figueras Aloy J, Grupo IRIS. Quality of life of preterm infants and admissions due to respiratory infections. An Pediatr (Barc) 2010; 73: 121-31. Spanish.
https://doi.org/10.1016/j.anpedi.2009.10.010

[11]   Vandenplas Y, Rudolph CD, Di Lorenzo C, *et al*. North American Society for Pediatric Gastroenterology Hepatology and Nutrition, European Society for Pediatric Gastroenterology Hepatology and Nutrition. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr 2009; 49: 498-547.

[12]   Bagucka B, De Schepper J, Peelman M, Van de Maele K, Vandenplas Y. Acid gastro-esophageal reflux in the 10 degrees-reversed-Trendelenburg-position in supine sleeping infants. Acta Paediatr Taiwan 1999; 40: 298-301.

[13]   Horvath A, Dziechciarz P, Szajewska H. The effect of thickened-feed interventions on gastroesophageal reflux in infants: systematic review and meta-analysis of randomized, controlled trials. Pediatrics 2008; 122: e1268-77.
https://doi.org/10.1542/peds.2008-1900

[14]   Vandenplas Y, Belli D, Benhamou P, *et al*. A critical appraisal of current management practices for infant regurgitation recommendations of a working party. Eur J Pediatr 1997; 156: 343-57.
https://doi.org/10.1007/s004310050613

[15]   Vandenplas Y, Leluyer B, Cazaubiel M, Housez B, Bocquet A. Double-blind comparative trial with two antiregurgitation formulae. J Pediatr Gastroenterol Nutr 2013; 57: 389-93.
https://doi.org/10.1097/MPG.0b013e318299993e

[16]   Tolia V, Lin C-H, Kuhns LR. Gastric emptying using three different formulas in infants with gastroesophageal reflux. J Pediatr Gastroenterol Nutr 1992; 15: 297-301.
https://doi.org/10.1097/00005176-199210000-00011

[17]   Billeaud C, Guillet J, Sandler B. Gastric emptying in infants with or without gastro-oesophageal reflux according to the type of milk. Eur J Clin Nutr 1990; 44: 577-83.

[18]   Vandenplas Y, Cruchet S, Faure C, *et al*. When should we use partially hydrolysed formulae for frequent gastrointestinal symptoms and allergy prevention? Acta Paediatr 2014; 103: 689-95.
https://doi.org/10.1111/apa.12637

[19]   Higginbotham TW. Effectiveness and safety of proton pump inhibitors in infantile gastroesophageal reflux disease. Ann Pharmacother 2010; 44: 572-6.
https://doi.org/10.1345/aph.1M519

[20]   Van der Pol RJ, Smits MJ, van Wijk MP, Omari TI, Tabbers MM, Benninga MA. Efficacy of proton-pump inhibitors in children with gastroesophageal reflux disease: a systematic review. Pediatrics 2011; 127: 925-35.
https://doi.org/10.1542/peds.2010-2719

[21]   ANSES. Saisine n° 2001-SA-0257. Rapport du comité d'experts spécialisé "eaux" concernant les critères de qualité des eaux minérales naturelles et des eaux de source embouteillées permettant une consommation sans risque sanitaire pour les nourrissons et les enfants en bas âge. [Report of a committee of experts specialized in "waters" concerning the quality criteria for bottled natural mineral waters and spring waters permitting their consumption with no risk to health by infants and young children]. 9 September 2003. www.anses.fr/fr/system/files/EAUX2001sa0257Ra.pdf. Accessed 15 March 2017.

[22]   Scholtens PA, Goossens DA, Staiano A. Stool characteristics of infants receiving short-chain galacto-oligosaccharides and long-chain fructo-oligosaccharides: a review. World J Gastroenterol 2014; 20: 13446-52.
https://doi.org/10.3748/wjg.v20.i37.13446

[23]   Coccorullo P, Strisciuglio C, Martinelli M, Miele E, Greco L, Staiano A. *Lactobacillus reuteri* (DSM 17938) in infants with functional chronic constipation: a double-blind, randomized, placebo-controlled study. J Pediatr 2010; 157: 598-602.
https://doi.org/10.1016/j.jpeds.2010.04.066

[24]   Tabbers MM, DiLorenzo C, Berger MY, *et al*. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition; North American Society for Pediatric Gastroenterology. Evaluation and treatment of functional constipation in infants and children: evidence-based

recommendations from ESPGHAN and NASPGHAN. J Pediatr Gastroenterol Nutr 2014; 58: 258-74.
https://doi.org/10.1097/MPG.0000000000000266

[25]   Wessel MA, Cobb JC, Jackson EB, Harris GS, Detwiller AC. Paroxysmal fussing in infancy sometimes called "colic". Pediatrics 1954; 14: 421-35.

[26]   Miller AR, Barr RG. Infantile colic. Is it a gut issue? Pediatr Clin North Amer 1991; 38: 1407-23.
https://doi.org/10.1016/S0031-3955(16)38227-X

[27]   Hyman PE, Milla PJ, Benninga MA, Davidson GP, Fleisher DF, Taminiau J. Childhood functional gastrointestinal disorders: neonate/toddler. Gastroenterology 2006; 130: 1519-26.
https://doi.org/10.1053/j.gastro.2005.11.065

[28]   Rhoads JM, Fatheree NY, Norori J, *et al*. Altered fecal microflora and increased fecal calprotectin in infants with colic. J Pediatr 2009; 155: 823-8.
https://doi.org/10.1016/j.jpeds.2009.05.012

[29]   Chau K, Lau E, Greenberg S, *et al*. Probiotics for infantile colic: a randomized, double-blind, placebo-controlled trial investigating *Lactobacillus reuteri* DSM 17938. J Pediatr 2015; 166: 74-8.
https://doi.org/10.1016/j.jpeds.2014.09.020

[30]   Savino F, Cordisco L, Tarasco V, *et al*. *Lactobacillus reuteri* DSM 17938 in infantile colic: a randomized, double-blind, placebo-controlled trial. Pediatrics 2010; 126: e526-33.
https://doi.org/10.1542/peds.2010-0433

[31]   Szajewska H, Gyrczuk E, Horvath A. *Lactobacillus reuteri* DSM 17938 for the management of infantile colic in breastfed infants: a randomized, double-blind, placebo-controlled trial. J Pediatr 2013; 162: 257-62.
https://doi.org/10.1016/j.jpeds.2012.08.004

[32]   Xu M, Wang J, Wang N, Sun F, Wang L, Liu X-H. The efficacy and safety of the probiotic bacterium *Lactobacillus reuteri* DSM 17938 for infantile colic: A meta-analysis of randomized controlled trials. PLoS One 2015; 10: e0141445.
https://doi.org/10.1371/journal.pone.0141445