Neonatal Antibiotics and Prematurity Are Associated with an Increased Risk of Functional Gastrointestinal Disorders in the First Year of Life

Silvia Salvatore, MD, PhD[1], Maria Elisabetta Baldassarre, MD[2], Antonio Di Mauro, MD, PhD[2], Nicola Laforgia, MD[2], Silvio Tafuri, MD, PhD[2], Francesco Paolo Bianchi, MD[2], Enzo Dattoli, MD[1], Lucia Morando, MD[1], Licia Pensabene, MD[3], Fabio Meneghin, MD[5], Dario Dilillo, MD[5], Valentina Mancini, MD[4], Valentina Talarico, MD[3], Francesco Tandoi, MD[1], Gianvincenzo Zuccotti, MD[5], and Massimo Agosti, MD[1]

Objective To assess the prevalence of functional gastrointestinal disorders (FGIDs) in the first year of life and the influence of different neonatal factors on development of FGIDs.

Study design A prospective cohort multicenter study including neonates, consecutively enrolled at birth, and followed up until 1 year. Gestational age, neonatal antibiotic administration, duration of hospitalization, mode of delivery, birth weight, and feeding pattern were recorded. FGIDs were classified according to Rome III criteria and assessed at 1, 3, 6, and 12 months of life.

Results Among 1152 newborns enrolled, 934 (81.1%) completed the study, 302 (32%) were newborns born preterm, 320 (34%) had neonatal antibiotics, and 718 (76.9%) had at least 1 FGID according to Rome III criteria (443 [47.4%] infantile colic, 374 [40.0%] regurgitation, 297 [31.8%] infant dyschezia, 248 [26.6%] functional constipation, and 34 [3.6%] functional diarrhea) throughout the first year of life. The proportion of infants born preterm presenting with FGIDs (86%) was significantly greater compared with infants born full term (72.5%) ($\chi^2 = 21.3$, $P = .0001$). On multivariate analysis, prematurity and neonatal use of antibiotics was significantly associated with at least 1 FGID.

Conclusions We found a high rate FGIDs in infants, likely related to the population recruited, the long observation period, the diagnosis based on Rome III criteria, and parental reports. Preterm delivery and neonatal use of antibiotics in the first months of life are associated with an increased incidence of FGIDs, particularly infantile colic and regurgitation. In our population, cesarean delivery and feeding pattern at 1 month of life emerged as additional risk factors for infant dyschezia and functional diarrhea. Other neonatal factors associated with FGIDs need to be further explored. *(J Pediatr 2019;■:1-8)*.

Functional gastrointestinal disorders (FGIDs) include a variable combination of chronic or recurrent gastrointestinal symptoms in the absence of structural or biochemical abnormalities. Despite heterogeneity in methods and definitions, many infants <12 months are affected by FGIDs, with a reported overall prevalence of 50% in newborns born full term and up to 73% with infantile colic and 87% with regurgitation in selected population.[1,2]

The 2006 Rome III criteria classified and clinically distinguished different FGIDs, in neonates and toddlers, including infant regurgitation, infant rumination syndrome, cycling vomiting syndrome, infant colic, functional diarrhea, infant dyschezia, and functional constipation.[3] FGIDs often have a negative impact on infants' and parents' quality of life, potential long-term health consequences, and increase in healthcare costs.[4]

The pathophysiology of FGIDs remains unclear. Different factors have been suggested as determinants, including genetic predispositions, psychosocial factors, abnormal intestinal motility, visceral hyperalgesia, gut inflammation, intestinal microbiota, early stressful events, and trauma.[5] There is evidence that early life events play a pivotal role in the programming of different diseases later in life.[6] Some authors speculated that the type of delivery, feeding practice, and early antibiotic administration may predispose infants to FGIDs.[7] We performed a prospective multicenter cohort study to investigate the possible relationship between neonatal factors (such as prematurity, antibiotic treatment, cesarean delivery, formula feeding, and hospital stay) and the development of FGIDs in the first year of life.

aRR	Adjusted relative risk
FGID	Functional gastrointestinal disorder
RR	Relative risk

From the [1]Unit of Pediatrics and Neonatology, "F. Del Ponte" Hospital, Dipartimento di Medicina e Chirurgia University of Insubria, Varese; [2]Department of Biomedical Science and Human Oncology, Aldo Moro University of Bari, Bari; [3]Department of Pediatrics, "Magna Graecia" University, Viale Pio X, Catanzaro; [4]Pediatric Unit, Saronno Hospital, Saronno; and [5]Department of Pediatrics, Vittore Buzzi Children's Hospital, University of Milan, Milan, Italy

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Methods

The study was carried out in 5 Italian pediatrics and neonatal units (Varese, Milano, Parma, Bari, and Catanzaro) between 2014 and 2016. The institutional review boards of participating hospitals approved the study protocol; written informed consent was obtained from parents of participants before inclusion.

Eligibility

Inclusion criteria were newborns born preterm (gestational age between 25 and 36 weeks) or newborns born at full term (gestational age ≥37 weeks) at the same participants hospitals, with Italian-speaking parents. Exclusion criteria were severe acute infection or neonatal complications; known genetic syndromes, congenital and/or malformative disorders; surgery; major neurologic, immune, metabolic, cardiac, or renal diseases; absence of parental consent; or language difficulty. All newborns satisfying inclusion and exclusion criteria were consecutively recruited during the first days of life.

Study Design

Gestational age, mode of delivery, neonatal complications, birth weight, antibiotic use during the first week of life, duration of hospitalization at birth, and feeding pattern at 1 month of life were collected in all newborns enrolled via hospital charts and direct interview of parents. At the time of the study, a validated questionnaire for FGIDs in infants was not available,[8] and the Rome IV criteria had not yet been published. Hence, FGIDs were clinically classified according to Rome III criteria[3] and assessed through a standardized interview to parents by a dedicated and ad hoc, trained physician at each hospital to promote uniform documentation. Data were collected using the same specific form at each clinical evaluation scheduled at 1, 3, 6, and 12 months. For newborns born preterm, a clinical evaluation was scheduled with the same time interval based on chronologic age. Review of hospital charts, outpatient clinic database, and a phone interview also were used for unclear or missing data during the follow-up period. Before starting the study, all participant investigators discussed the design of the study and reached a consensus on what to consider as FIGD and specifically infantile colic, dyschezia, regurgitation, functional diarrhea, and constipation, as well as data to be recorded.

Primary and Secondary Outcomes

The primary outcome was to assess the prevalence of FGIDs in a cohort of Italian infants born preterm and at term during the first year of life, using the Rome III Criteria (**Appendix 1**; available at www.jpeds.com). Secondary outcome was to investigate the possible association between FGID development and neonatal characteristics such as gestational age, mode of delivery, birth weight, antibiotics use during the first week of life, duration of hospitalization after birth, and feeding pattern at 1 month of life.

Statistical Analyses

The completed questionnaires were uploaded as an Excel spreadsheet (Microsoft, Redmond, Washington) and data were analyzed by Stata SE14 software (StataCorp LLC, College Station, Texas). Continuous variables were described as mean ± SD, categorical variables as proportions, with the indication of 95% CI where deemed appropriate.

Skewness and kurtosis tests were used to perform the normality analysis of continuous variables and it was not possible to set a normalization model. The Wilcoxon rank-sum test (nonparametric) was used to compare not-normal continuous variables between preterm and full-term births; the χ^2 test was used to compare the proportions between preterm and full-term births.

The association between FIGDs and gestation age (pre/full-terms), delivery mode, feeding pattern, antibiotics use during the first week of life, and duration of hospitalization after birth was assessed by means of univariate log-binomial regression analysis. The relative risk (RR) values were estimated, with 95% CI and test z score performed.

Subsequently, for each outcome, a multivariate log-binomial regression model was created, using as determinants the same variables used in the univariate log-binomial regression. The aRR (adjusted relative risk) values were estimated, with 95% CI and the test z score performed. For all the tests, a value of $P < .05$ was considered statistically significant.

Results

Of the 1152 newborns enrolled in the study, 934 (81.1%) completed the entire 12-month follow-up and were entered in the final analysis; 632 of 934 (67.7%) infants were born at full term and 302 of 934 (32.3%) were born preterm. Of the 632 infants born full term, 521 were born between 37 and 40 weeks of gestation, and 117 (18%) were post-term (eg, born at or beyond 41 weeks of gestation). Among the 934 infants who completed the study, 320 (34.3%) had antibiotics in the first week of life and 373 (39.9%) were born by cesarean delivery.

Demographic characteristics of participants are shown in **Table I**. As expected, infants born preterm showed significant difference in gestational age, birth weight, hospital stay, rate of cesarean delivery, rate of breastfeeding, and antibiotic use (**Table I**). Overall, in 718 of 934 participants (76.9%) at least 1 FGID was reported during the first 12 months of life, and in 369 (39.5%) infants, multiple FGIDs coexisted.

Infant colic and regurgitation were the most commonly recorded disorders, in 443 of 934 (47.4%) and 372 of 934 (40.0%) participants, respectively. Infant dyschezia, functional constipation, and functional diarrhea were reported in 297 of 934 (31.8%), 248 of 934 (26.6%), and 34 of 934 (3.6%) participants, respectively. Of these FGIDs, 99% of infantile colic, 96% of regurgitation and dyschezia, and 80% for functional constipation were reported during the first 3 months of life.

Table I. Demographic characteristics at baseline, according to the 2 groups of infants born preterm and full term

Variables	Preterm (n = 302)	Full term (n = 632)	Total (n = 934)	Test	*P*
Gestational age, d, mean ± SD	226.4 ± 20.2	277.7 ± 8.0	261.1 ± 27.4	z = 24.8	.000
Male, n (%)	140 (46.4)	300 (47.5)	494 (52.9)	χ^2 = 0.1	.750
Female, n (%)	162 (53.6)	332 (52.5)	440 (47.1)		
Cesarean delivery, n (%)	210 (69.5)	163 (25.8)	373 (39.9)	χ^2 = 163.0	.000
Vaginal birth, n (%)	92 (30.5)	469 (74.2)	561 (60.1)		
Birth weight, g, mean ± SD	1755.0 ± 626.2	3249.9 ± 416.3	2766.5 ± 856.2	z = 23.4	.000
Exclusive formula feeding at 1 mo, n (%; 95% CI)	162 (53.6; 47.8-59.4)	114 (18.1; 15.1-21.3)	276 (29.5; 26.6-32.6)	χ^2 = 181.7	.000
Exclusive breastfeeding at 1 mo, n (%; 95% CI)	46 (15.2; 11.4-19.8)	375 (59.3; 55.4-63.2)	421 (45.1; 41.9-48.3)		
Mixed feeding at 1 mo, n (%; 95% CI)	94 (31.2; 25.9-36.7)	143 (22.6; 19.4-26.1)	238 (25.4; 22.7-28.4)		
Antibiotic use, n (%; 95% CI)	179 (59.3; 53.5-64.9)	141 (22.3; 19.1-25.8)	320 (34.3; 31.2-37.4)	χ^2 = 124.0	.000
Hospital stay, d, mean ± SD	28.8 ± 22.4	4.7 ± 9.5	12.5 ± 18.7	z = 22.2	.000
Hospital stay				χ^2 = 440.4	.000
≤4 d, n (%)	31 (10.3)	521 (82.4)	552 (59.1)		
>4 d, n (%)	271 (89.7)	111 (17.6)	382 (40.9)		

Evolution of FGIDs during the clinical follow-up is shown in **Figure 1**. Among the 5 hospitals, the incidence of FGIDs as well as the percentage of neonates born preterm was not homogenous (**Appendix 2**; available at www.jpeds.com).

The proportion of infants born preterm (86.1%) presenting FGIDs throughout the study was significantly (χ^2 = 21.3, *P* = .0001) greater compared with infants born full term (72.5%). However, the average number of FIGDs was 1.9 ± 0.9, without any significant difference between groups (z = 0.3; *P* = .773; **Table II**).

We observed a significant difference in the proportion of infants affected by infant colic and regurgitation between the 2 groups of infants born preterm and full term (*P* < .05; **Table II**). Furthermore, the incidence of FGIDs among the infants born premature was significantly different based on different gestational age (χ^2 = 10.0; *P* = .012). However, regurgitation was reported more frequently in neonates born at 28-30 weeks compared with neonates born earlier (<28 weeks) or later preterm (**Table III**).

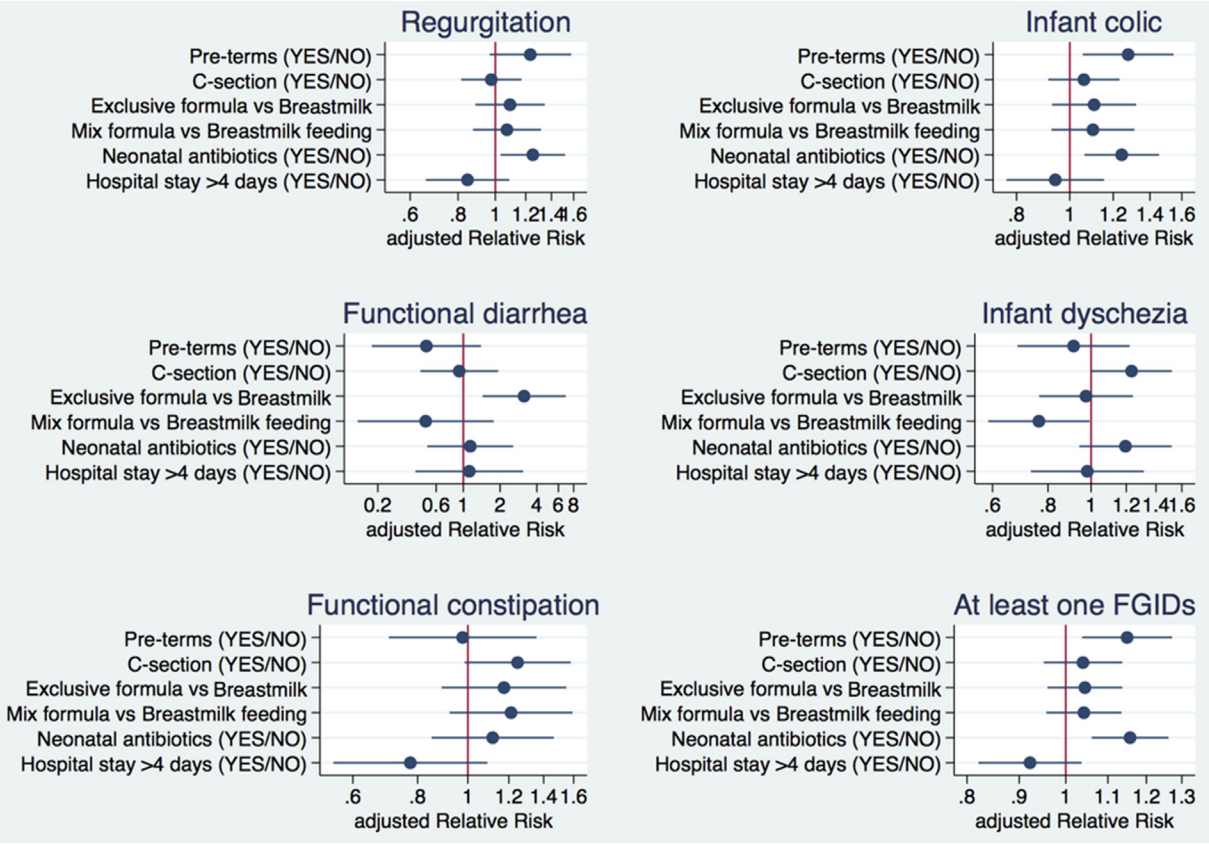

Figure 1. Multivariate analysis for risk factors associated with FGIDs.

Table II. Proportion (%) of infants with FIGDs, according to the different FIGD and group

Variables	Preterm (n = 302)	Full term (n = 632)	Total (n = 934)	Test	P
Regurgitation, n (%; 95% CI)	138 (45.7; 40.0-51.5)	236 (37.3; 33.6-41.2)	374 (40.0; 36.9-43.3)	$\chi^2 = 5.9$	**.015**
Infant colic, n (%; 95% CI)	178 (58.9; 53.2-64.5)	265 (41.9; 38.0-45.9)	443 (47.4; 44.2-50.7)	$\chi^2 = 23.7$	**.000**
Functional diarrhea, n (%; 95% CI)	10 (3.3; 1.6-6.0)	24 (3.8; 2.4-5.6)	34 (3.6; 2.5-5.0)	$\chi^2 = 0.1$	.711
Infant dyschezia, n (%; 95% CI)	98 (32.5; 27.2-38.0)	199 (31.5; 27.9-35.3)	297 (31.8; 28.8-34.9)	$\chi^2 = 0.1$	.768
Functional constipation, n (%; 95% CI)	80 (26.5; 21.6-31.8)	168 (26.6; 23.2-30.2)	248 (26.6; 23.7-29.5)	$\chi^2 = 0.0$	.976
At least 1 FIGD, n (%; 95% CI)	260 (86.1; 81.7-89.8)	458 (72.5; 68.8-75.9)	718 (76.9; 74.0-79.5)	$\chi^2 = 21.3$	**.000**
Number of FIGDs diagnosed, mean ± SD	1.9 ± 0.9	1.9 ± 1.0	1.9 ± 0.9	z = 0.3	.773

Variables in bold indicate statistical significance.

Finally, in a subset analysis we also found a significantly greater rate of regurgitation ($\chi^2 = 6.6$; $P = .010$) and at least 1 FIGD ($\chi^2 = 6.7$; $P = .010$) in infants born at or beyond 41 weeks of gestation compared with infants born between 37 and 40 weeks of gestation (Table IV).

Risk Factors for FGIDs

On univariate analysis (Table V), FGIDs were significantly associated with preterm birth (RR = 1.2; $P < .0001$), cesarean delivery (RR = 1.1; $P < .0001$), exclusive formula feeding (RR = 1.1; $P = .010$), use of neonatal antibiotics (RR = 1.2; $P < .0001$), and hospitalization longer than 4 days (RR = 1.1; $P < .0001$). In particular, regurgitation was significantly associated with preterm birth (RR = 1.2; $P = .013$) and use of neonatal antibiotics (RR = 1.2; $P = .007$); infant colic was associated with preterm birth (RR = 1.4; $P < .0001$), cesarean delivery (RR = 1.2; $P = .003$), exclusive (RR = 1.3; $P = .006$) or mixed formula feeding (RR = 1.2; $P = .011$), use of neonatal antibiotics (RR = 1.3; $P < .0001$), and hospitalization longer than 4 days (RR = 1.3; $P < .0001$). Functional diarrhea was associated only with exclusive formula feeding (RR = 2.4; $P = .014$). No other significant associations were found ($P > .05$).

Multivariate Analysis for Risk Factors Associated with FGIDs

On multivariate analysis (Table VI), prematurity and neonatal use of antibiotic was associated with at least 1 FGID (aRR = 1.2; $P = .001$). Regurgitation was significantly associated with use of neonatal antibiotics (aRR = 1.3; $P = .022$); infant colic with prematurity (aRR = 1.3; $P = .012$) and use of neonatal antibiotics (aRR = 1.2; $P = .006$); functional diarrhea with exclusive formula feeding (aRR = 3.1; $P = .004$), and infant dyschezia with cesarean delivery (aRR = 1.2; $P = .048$) and exclusive breast milk (aRR = 0.8; $P = .044$). No other significant associations were found ($P > .05$). Multivariate analysis for risk factors associated with FGIDs is shown in Figure 2.

Discussion

We found a high incidence of FGIDs in our cohort of infants prospectively evaluated from birth to 12 months of life and characterized by a high prevalence (32%) of newborns born preterm. Data on neonates born preterm with FGIDs are currently very limited, and this population often appeared in the exclusion criteria. However, as they are exposed to multiple factors suggested to influence gastrointestinal homeostasis, pain perception, and sensitivity,[5-7] we tried to enroll a high number of neonates born preterm, hypothesizing that they would be the most vulnerable population for the development of FGIDs. Moreover, in our population 320 (34.3%) had antibiotics in the first week of life and 373 (39.9%) were born by cesarean delivery, 2 additional factors partially related to our large proportion of newborns born preterm.

Approximately 75% of participants experienced at least 1 FGID; infantile colic and regurgitation were the most commonly reported gastrointestinal symptoms, occurring particularly in infants born preterm and in the first 3 months of life. To the best of our knowledge, this is the first study showing that both preterm delivery and neonatal use of

Table III. Proportion (%) of infants born preterm with FIGDs, according to the different gestational age at birth

Gestational ages, wk	Regurgitation		Infant colic		Functional diarrhea		Infant dyschezia		Functional constipation		At least 1 FIGD	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
<28 (n = 24)	10 (41.7)	22.1-63.4	17 (70.8)	48.9-87.4	1 (4.2)	0.1-21.1	10 (41.7)	22.1-63.4	7 (29.2)	12.6-51.1	23 (95.8)	78.9-99.9
28-30 (n = 60)	33 (55.0)	41.6-67.9	37 (61.7)	48.2-73.9	1 (1.7)	0.0-8.9	23 (38.3)	26.1-51.8	17 (28.3)	17.5-41.4	58 (96.7)	88.5-99.6
31-33 (n = 106)	44 (41.5)	32.0-51.5	58 (54.7)	44.8-64.4	3 (2.8)	0.6-8.0	33 (31.1)	22.5-40.9	26 (24.5)	16.7-33.8	88 (83.0)	74.5-89.6
34-36 (n = 106)	48 (45.3)	35.6-55.2	63 (59.4)	49.5-68.9	4 (3.8)	1.0-9.4	31 (29.3)	20.8-38.9	27 (25.5)	17.5-34.9	87 (82.1)	73.4-88.8
Test	χ^2	*P*	χ^2	*P*	χ^2	*P*	χ^2	*P*	χ^2	*P*	χ^2	*P*
	3.0	.391	2.4	.498	0.7	.848	2.4	.488	0.4	.934	10.0	.012

Table IV. Proportion (%) of infants born full term with FIGDs, according to the different gestational age at birth

Full term newborns gestational age	Regurgitation		Infant colic		Functional diarrhea		Infant dyschezia		Functional constipation		At least 1 FIGD	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Post-term (n = 117) 41-42 wk	56 (47.9)	38.5-57.3	56 (47.9)	38.5-57.3	5 (4.3)	1.4-9.7	40 (34.2)	25.7-43.5	34 (29.1)	21.0-38.2	96 (82.1)	73.9-88.5
Full term (n = 521) 37-40 wk	183 (35.1)	31.0-39.4	212 (40.7)	36.4-45.0	20 (3.8)	2.4-5.9	160 (30.7)	26.8-34.9	137 (26.3)	22.6-30.3	366 (70.3)	66.1-74.1
Test	χ^2	*P*	χ^2	*P*	χ^2	*P*	χ^2	*P*	χ^2	*P*	χ^2	*P*
	6.6	.010	2.0	.155	0.0	.794	0.5	.508	0.4	.542	6.7	.010

antibiotics determine an increased risk of the development of FGIDs in infants.

FGIDs are common disorders in adults and children. Gastrointestinal infection[9,10] and early life events such as gastric suction, cow milk protein allergy,[11] inflammation,[12] trauma,[13] and stress[14] have been suggested to predispose to visceral hyperalgesia and gastrointestinal symptoms later in life.[3,7,15] Two previous studies have assessed the prevalence of FGIDs in Italian infants, including a small group of newborns born preterm.[16,17] Iacono et al enrolled 2879 infants and showed that, in the first 6 months of life regurgitation, colic, constipation, and diarrhea occurred in 23%, 21%, 18%, and 4% of infants, respectively. The authors reported an increased prevalence of regurgitation in infants who had low birth weight and of diarrhea in newborns small for gestational age. However, the number of newborns born preterm was not specified, and Rome III criteria were not used.[16] Campanozzi et al recruited 2642 infants (27 infants born preterm) with a range of age from 0 to 12 months and followed them up at 6 or 12, 18, and 24 months. Regurgitation was reported in 12% of the population without a significant difference between the small group of infants born preterm and full term. Rome II criteria were used to classify functional regurgitation, no data on other FGIDs were recorded, participants were not recruited at birth, and the dropout of patients was nearly 30%.[17]

Vandenplas et al identified 30 studies on epidemiology of FGIDs in infants. In the first 6 months of age, approximately 1 of 2 infants shows at least 1 FGID.[1] Colic showed a worldwide prevalence ranging from 2% to 73%, regurgitation from 3% to 87%, functional constipation from 1% to 39%, and functional diarrhea and dyschezia <10%.

We found a greater incidence rate of FGIDs than in the previous studies.[1-3,16,17] This difference could be related to the characteristics of our population (one-third comprising infants born preterm, one-third comprising neonates submitted to antibiotic treatment in the first week of life, and 40% born by cesarean delivery) and to the definition and method of data collection. Moreover, it is noteworthy the long observation period with cumulative incidence of FGIDs derived by our prospective design assessing the occurrence of FGIDs from 0 to 12 months.

Although use of a validated diary, such as the Barr diary, would have been ideal and may have lowered the incidence of FGIDs in our population, it was not possible to have parents reliably complete this on a daily or weekly basis from 0 to 12 months.[18]

Table V. Univariate analysis for risk factors associated with FGIDs

Risk factors	Regurgitation		Infant colic		Functional diarrhea		Infant dyschezia		Functional constipation		At least 1 FGID	
	RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*
Preterm (yes/no)	1.22 (1.04-1.43)	**.013**	1.41 (1.23-1.60)	**.000**	0.87 (0.42-1.80)	.711	1.03 (0.84-1.26)	.767	1.00 (.79-1.25)	.976	1.19 (1.11-1.27)	**.000**
Cesarean delivery (yes/no)	1.06 (0.91-1.25)	.440	1.23 (1.07-1.40)	**.003**	1.05 (0.54-2.05)	.880	1.20 (1.00-1.45)	.053	1.20 (0.97-1.48)	.096	1.14 (1.07-1.22)	**.000**
Feeding pattern												
Exclusive formula vs breastmilk	1.15 (0.96-1.39)	.129	1.25 (1.06-1.46)	**.006**	2.42 (1.19-4.90)	**.014**	1.00 (0.81-1.25)	.956	1.14 (0.89-1.47)	.310	1.11 (1.03-1.21)	**.010**
Mixed feeding vs exclusive breastmilk	1.14 (0.94-1.38)	.190	1.24 (1.05-1.47)	**.011**	0.44 (0.13-1.56)	.205	0.79 (0.62-1.02)	.071	1.17 (0.90-1.52)	.233	1.08 (0.99-1.18)	.079
Neonatal antibiotics (yes/no)	1.24 (1.06-1.45)	**.007**	1.34 (1.17-1.53)	**.000**	0.92 (0.45-1.86)	.811	1.13 (0.93-1.37)	.219	1.02 (0.81-1.27)	.872	1.18 (1.10-1.26)	**.000**
Hospital stay >4 d (yes/no)	1.13 (0.96-1.32)	.132	1.31 (1.15-1.50)	**.000**	1.01 (0.52-1.98)	.973	1.05 (0.87-1.27)	.613	0.93 (0.75-1.16)	.506	1.14 (1.07-1.22)	**.000**

Variables in bold indicate statistical significance.

Table VI. Multivariate analysis for risk factors associated with FGIDs

	Regurgitation		Infant colic		Functional diarrhea		Infant dyschezia		Functional constipation		At least 1 FGID	
Risk factors	**aRR (95% CI)**	***P***	**aRR (95% CI)**	***P***	**aRR (95% CI)**	***P***	**aRR (95% CI)**	***P***	**aRR (95% CI)**	***P***	**aRR (95% CI)**	***P***
Preterm (yes/no)	1.23 (0.97-1.58)	.093	1.28 (1.06-1.55)	**.012**	0.50 (0.18-1.40)	.186	0.91 (0.68-1.22)	.541	0.98 (0.70-1.36)	.891	1.15 (1.04-1.27)	**.007**
Cesarean delivery (yes/no)	0.98 (0.81-1.17)	.795	1.06 (0.91-1.23)	.438	0.93 (0.45-1.93)	.840	1.23 (1.00-1.52)	**.048**	1.25 (0.99-1.58)	.066	1.04 (0.95-1.14)	.390
Feeding pattern												
Exclusive formula vs breastmilk	1.09 (0.89-1.35)	.405	1.11 (0.93-1.32)	.256	3.14 (1.44-6.88)	**.004**	0.9700 (0.76-1.24)	.832	1.17 (0.89-1.55)	.256	1.04 (0.96-1.14)	.316
Mixed formula vs breastmilk feeding	1.07 (0.87-1.31)	.501	1.10 (0.93-1.31)	.274	0.49 (0.14-1.77)	.279	0.76 (0.59-0.99)	**.044**	1.21 (0.92-1.59)	.168	1.04 (0.96-1.13)	.344
Neonatal antibiotics (yes/no)	1.25 (1.03-1.52)	**.022**	1.24 (1.06-1.45)	**.006**	1.14 (0.51-2.56)	.749	1.20 (0.94-1.52)	.144	1.12 (0.85-1.46)	.426	1.16 (1.06-1.26)	**.001**
Hospital stay >4 d (yes/no)	0.85 (0.66-1.09)	.192	0.94 (0.77-1.15)	.561	1.12 (0.41-3.09)	.827	0.98 (0.73-1.31)	.896	0.77 (0.55-1.09)	.144	0.92 (0.82-1.04)	.175

Variables in bold indicate statistical significance.

The diagnosis of FGIDs relies on clinical criteria, with exclusion of warning signs for organic diseases, because specific biomarkers or investigation are still lacking. Rome III and, more recently, Rome IV criteria provide a detailed classification of different FGIDs at different ages. However, a heterogeneity of diagnosis or misclassification among different physicians and an overestimation of prevalence of FGIDs cannot be excluded.

As multiple genetic and environmental factors, parental and physician perception, feeding patterns, and pharmacologic treatments appeared to be determinants in the rate of FGIDs in infants, our results should be cautiously considered and should be replicated in other preterm populations before a general conclusion can be drawn. The small number of previous studies assessing infantile dyschezia showed prevalence of <10% but according to a recent study, in 17% of infants symptoms preceding defecation were difficult to classify.[19] Constipation was reported in up to 39% of infants. However, another large prospective study is needed to determine whether our greater incidence of dyschezia reflects a specific figure of our population, a real increasing incidence of this disorder, a greater parental awareness, or a better classification from what was previously reported as functional constipation in infants.

Gastrointestinal symptoms often are distressing to the infant and parents, leading to a cascade of infant discomfort,

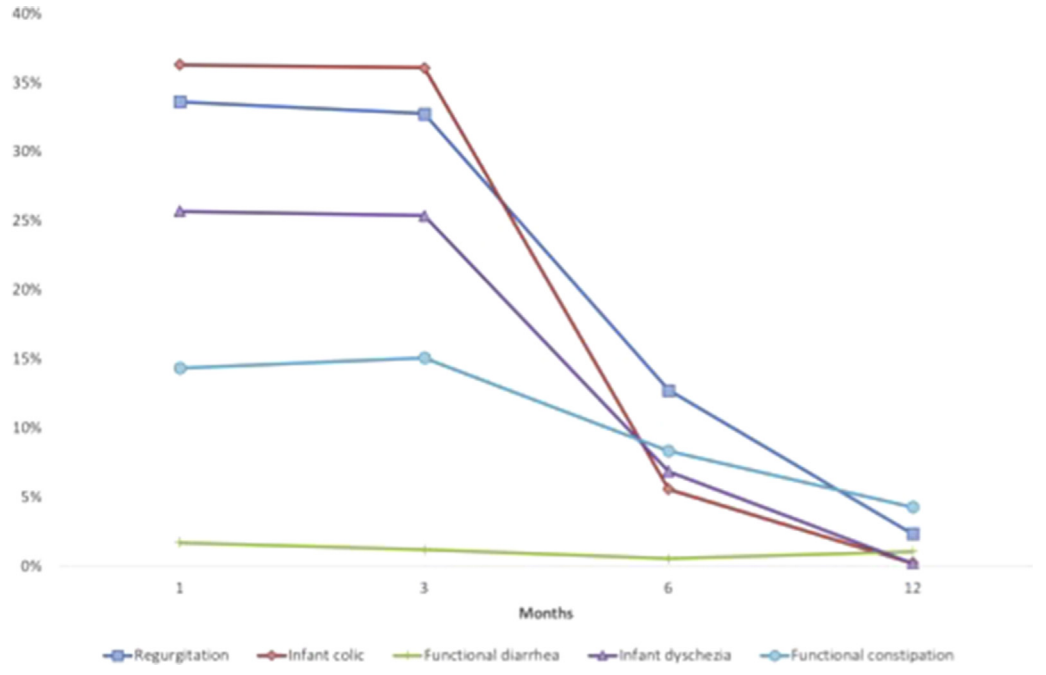

Figure 2. Temporal evolution of each FGID.

crying, parental anxiety, impaired quality of life, repeated healthcare professional consultations, and escalating healthcare costs.[4,8,20] Recognition of the exact prevalence of FGIDs is important to plan a tailored program of parents' education and clinical follow-up. Furthermore, identification of associated neonatal risk factors for FGIDs represents an essential prerequisite to develop possible early life interventions to decrease FGIDs later in life.[21,22]

This study simultaneously assessed the effect of different neonatal factors such as preterm birth, antibiotics therapy during the first week of life, hospital stay, type of delivery, and feeding pattern on to the development of FGIDs in infants. To limit the cumulative effect of different risk factors and to better clarify the major determinants for FGIDs, we performed both univariate and multivariate statistical analysis. Moreover, we tried to recruit a large group of newborns with different gestational ages and a subgroup of neonates born full term exposed to antibiotic treatment at birth for early life infection or for prevention of Group B Streptococcal disease.

Early-life antibiotic use recently has been linked to an increased risk of allergy[23,24] and of inflammatory bowel disease in genetically prone newborns.[25] Both infections and antibiotic early in life can determine immune dysregulation, aberrant barrier functions, microbiota modification, and altered gut sensorimotor functions that, in susceptible individuals, may lead to FGIDs.[12,26,27] Newborns born preterm represent an extraordinary population because of increased exposure to early life infections and antibiotics, traumatic and stress events, and prolonged hospital stay with often maternal deprivation, all possible predisposing factors for FGIDs. Noteworthy, the exposure of newborns born preterm to acute painful stimuli can, per se, prolong the period of hyperalgesia, which is one major determinant of FGID.[28,29]

If the results of our study are confirmed, a balanced strategy to reduce unnecessary neonatal antibiotic use and to promote intestinal homeostasis in at risk neonates should be considered. Nonetheless, parental education and reassurance on FGIDs and appropriate nutritional advice by healthcare professionals could reduce the inappropriate use of medication or dietary interventions later in life.[4]

Strengths of our study include a large population of neonates born both preterm and full term enrolled at birth and prospectively followed up to 12 months of life, the multicenter design, the analysis of different neonatal factors, and the use of Rome III criteria to classify FGIDs. A major limitation of our study is the lack of complete information about the antibiotic treatments at birth and during the follow-up period that did not allow a subgroup detailed analysis on this associated factor. Moreover, the occurrence of viral infections, probiotic administration, and other potential confounders such as neonatal gastric suction or other invasive procedures, exposure to smoke, daycare attendance, feeding characteristics, and family history of FGIDs were not considered. Other limitations were the possible influence of cow's milk protein allergy on FGIDs symptoms[30] and observer bias due to the unblinding of the participants healthcare professionals regarding the study outcomes. Finally, we fully relied on parents' reports, which generally overestimate infant's sympoms.[8] Further follow-up also is needed to determine whether FGIDs in infants persist into childhood, adolescence, and adulthood and if intervention in potential neonatal risk factor could reduce the burden of these diseases.[31-33]

The perinatal period, being the time during which maturation of the complex mechanisms that regulate the brain−gut−microbiota axis occurs, is a critical period in which different determinants may have important later consequences.[34] We showed that preterm delivery and neonatal use of antibiotics are significantly associated with an increased incidence of FGIDs, and particularly of colic and regurgitation in the first months of life. However, as the diagnosis of a FGID mainly relies on parental reports and interpretation of symptoms, a greater incidence in infants born preterm might be related to the coping style of parents, influenced by the multiple stressful experiences related to the preterm delivery.[35] Cesarean delivery, formula feeding, and longer hospital stay at birth may represent additional risk factors for FGIDs and need to be further analyzed. Clarifying the role of different potential risk factors during the neonatal period may provide new insights in the pathogenesis of FGIDs and indicate possible protective strategies. ■

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Reprint requests: Maria Elisabetta Baldassarre, MD, Department of Biomedical Sciences and Human Oncology, University of Bari - Policlinico, Piazza G. Cesare 11, Bari, 70124, Italy. E-mail: mariellabaldassarre@gmail.commariaelisabetta.baldassarre@uniba.it

Data Statement

Data sharing statement available at www.jpeds.com.

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