Management of the Most Common Functional Gastrointestinal Disorders in Infancy: The Middle East Expert Consensus

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ABSTRACT

The occurrence of functional gastrointestinal disorders (FGIDs) is a formidable challenge for infants, parents, and healthcare professionals. Although data from the Middle East are scarce, experts consider FGIDs a prevalent condition in everyday clinical practice. The new Rome IV criteria revisited the definitions from a clinical perspective to provide a practical and consistent diagnostic protocol for FGIDs. However, the treatment practices for functional disorders vary considerably among Middle Eastern countries, often resulting in mismanagement with unnecessary investigations and treatments. In addition, the role of various treatment modalities, including probiotics such as *Lactobacillus reuteri* DSM 17938, in FGIDs requires further discussion and evaluation. During a consensus meeting, a locally relevant approach for treating common FGIDs such as infant regurgitation, infant colic, and functional constipation was discussed and approved by regional experts. The participants suggested a simplified treatment plan and protocol for general pediatricians and other primary care physicians managing FGIDs. This easy-to-follow standardized protocol will help streamline the initial management of this complex disorder in the Middle East region and even globally.
INTRODUCTION

Functional gastrointestinal disorders (FGIDs) in infants encompass a variable combination of age-dependent, chronic, or recurrent symptoms not explained by structural or biochemical abnormalities [1]. As a condition that seems to merely exist as patient symptoms and parent interpretations, FGIDs pose a challenge to healthcare professionals, who are typically trained to gather palpable evidence of pathologies [1,2]. However, FGIDs are real for the affected infants and parents, and considering their high prevalence [1], gaining clarity on their diagnosis and treatment is of utmost importance. The Rome III criteria were updated recently to Rome IV with the aim of further refining and accommodating the practical aspects of the FGID diagnostic process [1].

FGID BURDEN

Prevalence estimates of FGIDs show wide variation in the published literature. According to clinical studies, 55% of infants show at least one FGID symptom from birth to 6 months [3]. Infant regurgitation is by far the most common FGID, present in up to 67% of infants and peaking at 4 months of age. Infant colic and functional constipation are also common during infancy, with a prevalence of up to 19% and 27%, respectively. Functional diarrhea is relatively uncommon among the four FGIDs, with a prevalence of up to 7% [1]. Experts from the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) conducted a literature review that identified 30 studies that reported the prevalence of FGIDs in infants under 12 months of age and determined the average prevalence of infant regurgitation, colic, and constipation as 30%, 20%, and 15%, respectively [4]. The overall prevalence of FGIDs with the new Rome IV criteria was more or less similar to the rates reported with the Rome III criteria [5,6]. In addition, although FGIDs are generally described as separate entities, as many as 78% of infants with FGIDs may present with more than one disorder, with colic being the most frequent concomitant disorder [7,8].

Although clear estimates from the Middle East and North Africa (MENA) region are lacking, available data point toward a much higher prevalence of FGIDs. In a recent survey of pediatricians from the MENA region, the majority of the participants stated that the prevalence of infant colic <4 months of age exceeded 40% [9]. A survey of Saudi mothers found that their major reasons for changing an infant formula were colic and gas (32%), constipation (23.6%), and gastroesophageal reflux (20.4%) [10].

FGIDs impair infant and parent quality of life and may have a lasting impact on later life. Regurgitation can negatively impact infant quality of life due to food refusal, crying, back arching, and irritability [11]. Frequent regurgitation during infancy increases the risk of heartburn, vomiting, and acid regurgitation at 9 years of age [12]. There are several reports of potential associations between infant colic and later health outcomes, including recurrent abdominal pain, sleep disorders, aggression, fussiness, and migraine [13,14]. Colic and excessive or inconsolable crying can also lead to poor mother–child interactions, postpartum depression, social isolation, parental frustration, exhaustion, and an increased risk of child abuse [15-18].
WHO IS AT RISK OF DEVELOPING FGIDS IN EARLY CHILDHOOD?

Despite a lack of validated risk stratification tool for FGIDs, increased prevalence was observed in only-children, firstborns, and infants with divorced or separated parents [19]. Preterm delivery and neonatal use of antibiotics in the first few months of life were also associated with FGIDs, particularly infant colic and regurgitation. Cesarean delivery and feeding patterns at 1 month of life emerged as risk factors for infant dyschezia and functional diarrhea [20]. Living in an urban area and being underweight for one’s age were proposed to be significantly associated with functional constipation (Table 1) [21]. It is also interesting to note that male and female infants show a comparable prevalence of FGIDs [7,19] in contrast to the female preponderance seen in older children [22].

CLINICAL PRESENTATION AND DIAGNOSIS OF FGIDS

Common FGIDs such as infant regurgitation, infant colic, dyschezia, functional diarrhea, and functional constipation may start very early in life [1]. A clear objective diagnosis may facilitate the acceptance of an FGID diagnosis by the parents, especially considering the apparent lack of a causative organic pathology [23]. Key diagnostic recommendations per the Rome IV criteria for some of the commonly encountered FGIDs in infants <12 months of age are given below [1]. Since infant diarrhea is a relatively complicated disorder in primary care, the criteria for functional diarrhea are not discussed here.

**Infant regurgitation**

Infant regurgitation is characterized by gastroesophageal reflux, which is sufficiently high to be visualized. Regurgitation must be differentiated from similar disorders such as vomiting and rumination as well as gastroesophageal reflux disease, which is diagnosed when regurgitation causes complications or contributes to tissue damage or inflammation [1].

An objective diagnosis of infant regurgitation requires both of the following criteria in otherwise healthy infants at 3 weeks to 12 months of age [1]:

1. Regurgitation two or more times per day for 3 or more weeks; and
2. No retching, hematemesis, aspiration, apnea, failure to thrive, feeding or swallowing difficulties, or abnormal posturing.

**Infant colic**

Infant colic has been described as a behavioral syndrome in infants involving long periods of crying and hard-to-soothe behavior [1].

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**Table 1. Potential risk factors or associations for functional gastrointestinal disorders [19–21]**

| Risk Factor/Situation |  |
|-----------------------|--|
| Cesarean delivery      |  |
| Preterm delivery       |  |
| Neonatal use of antibiotics | |
| Being an only child    |  |
| Being the firstborn child |  |
| Having divorced or separated parents | |
| Living in an urban area |  |
| Being underweight for age |  |
An objective clinical diagnosis of infant colic requires that the infant meet all three of the following criteria [1]:

1. <5 months of age when the symptoms start and stop;
2. Recurrent and prolonged periods of crying, fussing*, or irritability reported by caregivers that occur without obvious cause and cannot be prevented or resolved by caregivers; and
3. No evidence of failure to thrive, fever, or illness.

*Fussing refers to intermittent distressed vocalization and has been defined as “[behavior] that is not quite crying but not awake and content either.” Infants often fluctuate between crying and fussing, making it difficult to distinguish between the two symptoms in practice.

**Functional constipation and dyschezia**

Functional constipation is often the result of repeated attempts by a child to withhold feces in an attempt to avoid unpleasant defecation. This withholding behavior leads to stool retention, which leads the colon to absorb more water and create hard stools [1].

A diagnosis of functional constipation in infants requires 1 month of at least two of the following [1]:

1. Two or fewer defecations per week;
2. History of excessive stool retention;
3. History of painful or hard bowel movements;
4. History of large-diameter stools; and
5. Presence of a large fecal mass in the rectum.

Functional constipation should not be confused with infant dyschezia, which represents poor coordination between increased intra-abdominal pressure and relaxation of the muscular pelvic floor during defecation [1,24]. Infants with dyschezia strain for many minutes, scream, cry, and turn red or purple in the face with each attempt to defecate. They pass stools several times daily rather than demonstrating constipation, characterized by two or fewer defecations per week [1].

The diagnostic criteria for dyschezia in infants <9 months of age are as follows [1]:

1. At least 10 minutes of straining and crying before the successful or unsuccessful passage of soft stools; and
2. No other health problems.

In the majority of infants, the symptoms of dyschezia begin in the first few months of life and resolve spontaneously after 3–4 weeks [1]. Since there is no management for dyschezia except reassurance, we recommend referring the child to a pediatric gastroenterologist to confirm the diagnosis. This entity is not included in the consensus statement.

**Functional diarrhea**

Functional diarrhea is defined by the daily painless recurrent passage of three or more large unformed stools for 4 or more weeks with onset in the infant, toddler, or preschool years [1]. Considering that the occurrence of chronic or recurrent diarrhea in infancy can be due to many serious organic disorders, the recommended approach to its management is to refer the child to a pediatric gastroenterologist. Hence, we have not included it in this consensus statement.

Although several treatment guidelines and protocols are available for the management of FGIDs in infancy [25-27], certain practical aspects, such as the differential management
of exclusively breastfed infants versus formula-fed infants with FGIDs, remain ambiguous. Moreover, the guidelines do not provide the definitive duration of all arms of the treatment protocols or algorithms. These gaps provide room for individual interpretation and practice and may lead to inconsistent treatment practices among healthcare professionals. The Middle East FGID Consensus meeting was organized to generate a simple, definitive, and practical recommendation for clinicians managing FGIDs in this region.

METHODS

For the development of a regional consensus, 14 leading experts from Bahrain, Iran, Jordan, Kuwait, Lebanon, Oman, Saudi Arabia, and United Arab Emirates convened a meeting. A structured quantitative method was employed to facilitate the discussion and reach a consensus [28]. Statements were prepared before the consensus meeting based on local clinical practice and discussions with experts from the region. Before the vote, each statement was extensively discussed within the group and amended. All group members voted anonymously, and a 10-point scale was used to quantify the consensus (0=strongly disagree to 9=fully agree). A vote of 6 or greater meant “agreement,” while a vote of 9 was considered an expression of stronger agreement than a vote of 6. Consensus was considered achieved if more than 75% of the votes were 6, 7, 8, or 9.

CONSENSUS RECOMMENDATIONS

This expert discussion focused on managing FGIDs in healthy term infants <12 months of age. FGIDs in preterm infants, toddlers, or older children were not discussed in this opinion. The experts agreed that FGIDs are a frequently encountered challenges in everyday clinical practice despite the apparent lack of formal epidemiology figures from the region. There is consensus that a concerted effort is needed to estimate the burden of FGIDs in the region. As with any functional disorder, parental and caregiver reassurance, counseling, support, and education are integral aspects of the management of infantile FGIDs [1]. The risk stratification of FGIDs has been discussed as a potential tool to help identify and prevent the disorder in at-risk infants. The experts also opined that the role of allergy in FGIDs and its management is a separate topic in itself and beyond the scope of this discussion.

Infant regurgitation

Warning signs such as severe vomiting, irritability, crying, fussiness, feeding problems, atopic dermatitis, constipation, diarrhea, failure to thrive, hematemesis, back arching, neurological abnormalities, and/or neurodevelopmental delay should be ruled out as a first step in the management of infant regurgitation [25,29]. Considering the evidence of probiotics offering a better gastric emptying rate and other potential benefits in the treatment of regurgitation [30,31], the experts opined that a trial of a thickened formula with added Lactobacillus reuteri DSM 17938 may be an option for the management of infant regurgitation (Table 2, Fig. 1).

Infant colic

The experts discussed available evidence for the management of infant colic, including clinically significant data for the probiotic L. reuteri DSM 17938 (Table 3) [32-35]. There was a strong consensus within the group that this specific probiotic strain is an option for
the management of infant colic (Table 4, Fig. 2). The experts felt that the role of lactose avoidance in infant colic is debatable because of the lack of clinical evidence and should not be recommended as a routine treatment.

**Functional constipation**

The experts recommended the early administration of oral laxatives for the management of functional constipation. Considering the limited available evidence and proven safety profile
[36,37], there was a weak recommendation for the management of functional constipation using the probiotic *L. reuteri* DSM 17938, which did not meet the consensus criteria (Table 5). Although this indication differs from that stated in the ESPGHAN and NASPGHAN guidelines, the experts opined that the latest scientific evidence points toward the potential benefits of *L. reuteri* DSM 17938 in the management of functional constipation [38]. Hence, the panel concluded that while the main treatment for functional constipation remains oral laxatives, *L. reuteri* DSM 17938 is the most studied strain to date and a viable option if a probiotic is being considered in combination with oral laxatives for the treatment of this FGID.

**DISCUSSION**

Pharmacotherapy is not recommended for the management of FGIDs such as infant regurgitation and colic due to a lack of evidence and the potential risk of adverse events [26,39,40]. Potential conservative treatments for regurgitation include upright positioning after meals and thickened feedings. Evidence is limited for positioning [41-45], and even
considering the possible benefits, positioning and elevating the head of the crib are not recommended by ESPGHAN, NASPGHAN, or the American Academy of Pediatrics because of the risk of sudden infant death syndrome [26,46,47]. Thickened feedings and antiregurgitation formulas, especially those with digestible carbohydrates, can decrease regurgitation in healthy infants without interfering with their nutrition [48,49].

The first step in the management of colic is to rule out important warning signs such as severe vomiting, back arching, gastrointestinal bleeding, failure to thrive, abdominal distention, bloating, and any other signs of further organic causes [25]. Evidence from several randomized controlled trials and systematic reviews supports the use of a particular probiotic supplement (L. reuteri DSM 17938) to reduce infant crying due to colic (Table 3) [32-35].
It is important to rule out serious disorders such as Hirschsprung’s disease and cystic fibrosis in infants presenting with constipation. The goal of treatment is to facilitate painless defecation until a regular defecation pattern is restored and the cycle of pain and hard stools is broken [1,25]. Nonstimulant laxatives such as polyethylene glycol (PEG), lactulose, or Milk of Magnesia may be considered for the initial management of functional constipation [1]. PEG should be considered in infants older than 6 months of age [25]. There is limited published information on the treatment of infant constipation with probiotics; however, it is considered safe in infancy [1,36,37]. Experts agree that constipation in infancy is a relatively more difficult and serious disorder since it may be the manifestation of a serious medical/organic disorder. A simple protocol and treatment flowchart for functional constipation was deemed counterproductive by the participating experts; therefore, it was not included in this paper.

Available evidence suggests that colic, constipation, and regurgitation may be associated with cow’s milk allergy (CMA), which must be excluded [50-52]. Readers are recommended to always consider the possibility of CMA in an infant presenting with FGID and, in case of a possible allergic etiology, follow an accepted management guideline for CMA.

**CONCLUSION**

Regularly updated tools such as the Rome IV criteria will be of great assistance in the clinical diagnosis of FGIDs in infancy. As a next step, we developed a simple and practical treatment protocol for primary care physicians and general pediatricians, who are usually the initial point of contact for the parents of infants with FGIDs. With the right utilization of the latest Rome criteria and our treatment plan, we hope that clinicians in our region will be empowered to provide a positive diagnosis and follow it up with a unified and effective treatment strategy for patients suffering from these challenging disorders in early life.

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