Infantile Colic: An Update

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ABSTRACT

Context: Infantile colic is self-limiting condition but it can be a cause of anxiety for parents and challenge for doctors. The challenge for the doctors lies in correct identification of the condition and appropriate management. The objective of this review article is to summarize the pathophysiology, treatment options and outcome in infantile colic so that clinicians can have a fair idea about the condition, recent updates and future prospective.

Evidence: A search of The Cochrane Library, PubMed, Google Scholar was made using the key words "Infant colic", Infantile colic", "excessive crying in infants". All the materials were analyzed and summarized.

Results: At present infantile colic is an area of clinical research both in terms of etiology and treatment. Various etiological theories have been proposed but none of them are strong enough to completely describe the condition. Various treatment agents are being tried for colic like counseling and behavioral modification, dietary modification, lactase and probiotic supplementation, pain relieving agents, and chiropathy. Proper counseling of the parents is the first line of management at present. Simethicone has no role in decreasing the symptoms of colic and Dicyclomine is not recommended in children younger than six months. No specific recommendations have been made on the use of pain relieving agents and manipulative therapies in colic. At present strong evidence is lacking regarding the use of probiotics, lactase supplementation and dietary modification.

Conclusion: Counseling of parents about the benign nature of the condition is considered first line for now until an effective treatment is established. Other treatment options are prescribed on a case-based manner and parental perception of the condition.

Keywords: *Counseling, Crying, Colic, Infant, Lactase, Probiotics.*

Crying is an essential behavior to communicate the demands of the baby so that it can be fulfilled by the caregiver. Crying is a good signal that child is in need but a poor signal of what the child needs. Prolonged crying or fussing, particularly unsoothable crying is a source of anxiety and distress for the parents, and challenge for the doctor. Infant colic is a diagnosis of exclusion for prolonged cry in early infancy. It is described as compulsive and paroxysmal crying or fussing with multi-factorial etiology. It is considered as a behavioral syndrome of early infancy and a normal variant of crying curve in infancy [1].

[DEFINITION]

The classic definition of infant colic was given in 1954 by Wessel [2], in 1954 who described colic as a condition occurring in an otherwise healthy, well-fed infant with crying or fussing for more than three hours a day, for more than three days a week and for more than three weeks. The need for modification of Wessel's criteria was realized later because it was not practical to ask parents to wait for three weeks to arrive at a diagnosis. Hence modified Wessel's criteria was given in which the duration of symptom was reduced from three weeks to one week. But this definition failed to address pub benign nature of the condition and babies were referred to experts in view of excessive crying. To avoid unnecessary diagnostic and therapeutic misadventures the need for recognition of colic as a functional disorder was felt and thus infant colic was classified as a functional gastrointestinal disorder (FGID) under Rome diagnostic criteria (ROME) III criteria. FGID comprise of chronic/ recurrent symptoms that occur in the absence of any anatomic abnormality/ inflammation or tissue damage. The ROME III criteria for infant colic is for infants from birth to four months and must include paroxysms of irritability, fussing/crying that starts and stops without any obvious cause, episodes lasting three or more hours a day, occurring three days a week for at least one week and no failure to thrive [3]. But soon the flaws in ROME III criteria were recognized. The three-hour cut-off for crying or fussing was arbitrary and an infant who cried for 2 hours and 50 minutes was no different from an infant who cried for three hours a day. Moreover crying peaks by five to six weeks of age and a three hour cut off for a four month baby for whom the peak has already occurred was not correct. Also maintaining a Cry-record for seven days was practically not possible for most parents. Thus the ROME IV criteria was given in 2016, in which diagnostic criteria was given for clinical purpose and additional criteria was given which had to be satisfied for research proposes [4]. The ROME IV criteria are "An infant who is less than five months of age when symptoms start and stop; recurrent and prolonged periods of infant crying, fussing or irritability reported by caregivers that occur without any obvious cause and cannot be prevented or resolved by caregivers; no evidence of infant failure to thrive, fever or illness" [4]. Here "fussing" refers to intermittent distressed vocalization and has been defined as " (behavior) that is not quite crying but not awake and content either [4]." Infants often fluctuate between crying and fussing, so that the two symptoms are difficult to distinguish in practice. For clinical research purposes, a diagnosis of infant colic

must meet the preceding diagnostic criteria and also include: Caregiver reports infant has cried or fussed for three or more hours per day during three or more days in seven days in a telephone or face-to-face screening interview with a researcher or clinician, and total 24-hour crying plus fussing in the selected group of infants is confirmed to be three hours or more when measured by at least one prospectively kept, 24-hour behavior diary [4]. Thus colic is a disease of well thriving infant with no underlying disease.

Salient features of ROME IV criteria are that instead of using the duration of crying for diagnosis, it considers the crying behavior which causes distress to parents, and provides separate criteria for clinical use and research (*Table* I). Even though the classical three-hour cut-off is considered arbitrary and not used for clinical criteria, this has been retained for research purpose.

[EPIDEMIOLOGY]

The prevalence of infant colic varies greatly depending on the criteria used in the study, type of study conducted, method of data collection (community-based/ hospital record-based), and the population studied (*Table* II). Global prevalence of infant colic is estimated to be around 20%, but most of the research has been done in Western population [5]. A systematic review of 39 randomized control trials on infant colic reported that 20 different definitions of infant colic were used and the outcome criteria were also not uniform [6]. A systematic review of literature done in 2001 (before publication of ROME III criteria) revealed that occurrence rate of infant colic in prospective studies varied from 3% to 28% and in retrospective studies between 8% to 40% [7]. In this review, two prospective studies of high quality which used Wessel's criteria for definition had a prevalence of 5% and 19%, respectively [8,9]. Canivet, *et al*. [8] conducted a retrospective as well as prospective study on colic and found that retrospective studies had higher prevalence even though the definition of colic was similar. Van Tilburg, *et al*. [10] determined the prevalence of Functional gastrointestinal disorders (FGID) in US population as reported by parents, and reported it to be 5.9%. Similarly in a cross-sectional study, Liu, *et al*. [11] used ROME III criteria and found a prevalence of 1.4% in China. With the publication of ROME III it became the new standard and prevalence studies were based on it. Community-based studies are expected to yield better results than hospital-based studies because only a fraction of the parents approach the health care facilities and the child rearing practices differ among communities. Thus a well-structured study involving population representative of different parts of the world and using uniform criteria is needed to know the exact prevalence of the condition.

[PATHOPHYSIOLOGY]

Several theories have been proposed relating various factors to infant colic, but none of these theories have sufficient evidence to establish causation colic. The word colic points towards the gastrointestinal origin but even the classical Wessel definition does not mention it as a discomfort originating from gut. There is no proof that the source of discomfort in infants with colic is gut but for ease these theories can

be broadly classified as non-gastrointestinal or gastrointestinal. The non-gastrointestinal causes of colic include behavioral causes, altered parent-child interaction, immaturity of CNS, and early form of migraine. The gastrointestinal causes of colic include developmental lactose intolerance, altered gut microorganism, immaturity of enteric nervous system, increased motilin receptors or cow milk hypersensitivity. It has been shown that the early mode of enteral nutrition does not affect the incidence of colic that is whether the child is breast fed or bottle fed does not affect the incidence of colic. The widely reviewed etiology now is relating to gastrointestinal causes which includes lactase deficiency in early infancy and altered gut microorganisms.

Non-Gastrointestinal Causes

The word colic imparts unwarranted emphasis on the gastrointestinal etiology even though no such evidence exists. Various non-gastrointestinal theories for colic have been proposed which can be broadly classified as factors relating to mother, baby and environment. Factors related to mother include maternal age, educational background, smoking, alcohol consumption, antenatal maternal stress and anxiety, poor feeding techniques [17]. Maternal smoking in pregnancy has been shown as a risk factor for colic. Poor feeding techniques lead to a hungry unsatisfied infant. Factors related to baby include difficult infant temperament, way to maintain normal homeostasis, immaturity of central nervous system, early form of migraine. Factors related to environment include lack of family support and family stress. The behavioral cause states that altered parent child interaction can be a cause of colic. It has been proposed that misinterpretation of infant cries lead to ineffective caregiver responses which lead to unsatisfied infant. A new concept has come which states that colic is due to CNS immaturity and colic can be a form of migraine [18].

Gastrointestinal Causes

Lactose Intolerance: It has been observed that patients with lactose intolerance have high hydrogen content in the expired air after an oral lactose challenge [19]. Lactase is an enzyme present in the small intestine which is responsible for digestion of lactose. When lactase enzyme is deficient, lactose escapes digestion in small intestine and reaches large intestine where the colonic microorganisms act on it and lead to its fermentation and hydrogen production. The hydrogen gas is absorbed in the blood stream, reaches the lungs and is expired through the nose which is then measured by gas chromatography technique. The hydrogen breath test is used as a non-invasive tool for detection of carbohydrate intolerance (lactose, fructose) and small intestinal bacteria overgrowth. In lactose breath hydrogen test rise in breath hydrogen by 20 ppm above basal level after lactose ingestion is considered positive [19]. The theory relating infant colic to lactase deficiency suggests that lactase deficiency in early infancy leads to lactose malabsorption and increased gas production which in turn acts as a source of discomfort for

infants [20]. It is also supported by the observation by Illingworth [21] that such cries are relieved by flatulence. It has been shown that infants with colic have more hydrogen content in the breath as compared to non-colicky infants after ingestion of milk [22]. However, this theory fails to explain the fact that infants with colic cry more during evening even though their main diet is lactose rich milk (either breast milk/ formula feed). In some studies it has been proposed that infants, including preterm, have sufficient amount of lactase to digest the milk [23]. They found that the lactase activity of the newborn is equal to the immediate demands of milk feeding, but after five days of age. It has been proposed that even infants with primary lactase deficiency can tolerate some milk without producing symptoms. In a study conducted by Liebmann, *et al*. [24], babies with colic did not have reduced stool pH and positive stool reducing substance test. Thus the association between lactose intolerance and colic is yet to be established.

Altered gut flora:

Alteration in gut microorganism or more correctly decrease in commensal bacteria like *Lactobacillus* and *Bifidobacter* in gut of babies as a reason for colic and as a treatment option is gaining momentum. It was known earlier that there were differences in gut flora between colicky and non-colicky infants [25]. Weerth, *et al.* [26] revealed that there was significant difference in intestinal flora in infants with and without colic even by the age of one week, *i.e.*, that is even before the onset of symptoms. Infants with colic had slower colonization, lower diversity and stability of gut microorganism, increased concentration of *Proteobacter*, and decreased concentration of *Lactobacillus*, *Bifidobacter* and other butyrate producing bacteria [26]. In this study, it was suggested that early detection of change in gut microorganism can be used for preventive strategy *i.e.*, probiotic supplementation even before the onset of colic in infants or even antenatal supplementation to mothers. More research is required to accept this suggestion. The micro-organism reported most recently to be associated with infant colic is *H. pylori* [27]. In a study conducted in Egypt to determine the relation of *H. pylori* with colic, it was found that *H. pylori* stool antigen test was positive in 81.8% of infants with colic and 23.3% of infants without colic [27]. It was suggested that *H. pylori* alters the host immune response which in turn leads to non-commensal bacterial colonization and altered gut micro flora [27].

The other gastrointestinal theories proposed for infant colic are: immaturity of enteric nervous system which leads to intestinal contraction and colic, increased motilin receptors which causes intestinal hyper-peristalsis, and cow milk hypersensitivity. Some children, especially with family history of atopy, are sensitive to cow milk protein. This entity must be differentiated from lactose intolerance because lactose intolerance causes only a symptomatic disease but cow milk protein allergy can cause damage to intestinal epithelium. Evidence shows that 25% of infants with moderate to severe symptoms have cow milk protein dependent colic.

[CLINICAL FEATURES]

The classical presentation is an over-anxious parent with an inconsolable infant. Parents usually say that the colicky cry is different from other cries and describe these cries to be more urgent, piercing and making them feel that baby is in pain [28]. These cries are associated with hypertonia, facial flushing, withdrawal of legs towards abdomen and flatulence. The crying starts and stops abruptly. Assessing an infant during an episode of colic may indicate that the baby is in moderate to severe pain as per FLACC score, a pain scoring system for infants [29]. Infant colic begins by 2 to 3 weeks of age, peaks by 6 weeks and resolves by 3 months [1]. There is no sex predisposition [17,30] but familial predisposition has been suggested [30]. In most of the studies the incidence of colic has shown to be not related to the mode of enteral nutrition of baby or position of baby on the breast [17,31,32], but some authors report that breastfeeding was a protective factor [33]. In contrast, in a study conducted in Turkey on infants with colic, 83.3% of infants were breast fed [34]. This difference might be due to selection bias as most of the children in this study were breastfed as compared to mixed-fed and top-fed infants. Even though the benign nature of infant colic, it is important for the doctor to identify the condition because prompt counselling of parents about the benign course will avoid unwarranted diagnostic intervention in the baby and anxiety and self-doubt in the parents.

[DIAGNOSTIC TOOLS]

There are various tools for analysis of crying in infants but none have been proven useful for clinical purpose. Validity of these tools is an area for clinical research. Tools such as Barr Baby Day Diary, Ames Cry Score, Parental Diary of Infant Cry and fuss Behavior, Crying Pattern Questionnaire, Infant Colic Scale have been used for research purposes and there are no recommendations for use of these scales for clinical purpose, other than for research [35]. Most of these tools are based on "crying" as the main factor. Barr baby day diary is the most studied tool. In this diary, each day was divided into four time rulers representing night, morning, afternoon and evening. Each time ruler was further divided into six divisions representing six hours. The smallest time division which could be represented in this diary is five minutes. These time rulers have to be shaded by the parents according to infant behavior: sleeping, awake and feeding, awake and content, awake and fussing, awake and crying, awake and sucking [36]. Ames cry score is a simpler score which consists of three questions with four responses which are scored from 0-3. A total score of more than three is considered as colic [37]. A tool which was developed with a novel insight was Infant Colic Scale by Ellet, *et al.* [38]. It was based on the five etiological theory of colic namely: cow milk/ soy protein allergy/ intolerance; immature gastrointestinal system, immature central nervous system, difficult infant temperament and parent-infant interaction problem. After publication of ROME III criteria for FGID, a functional questionnaire was developed [3]. Under ROME IV, questionnaire for pediatric research and epidemiological purpose of FGID has been developed and is

available online (R4PDQ – Toddler: parent report form for infant and toddler) [4]. Questions of ROME IV criteria are based on the definition of colic and include the age, crying behavior and weight gain of the child and presence or absence of fever.

[TREATMENT]

The main treatment of infant colic is first excluding all causes of excessive crying in an infant followed by counseling and reassurance of the parents. The cause of excessive cry can be as simple as diaper poking the baby to CNS infections leading to shrill cry. It is emphasized that colic is a diagnosis of exclusion in a well thriving infant and if a baby is visibly sick, diagnosis of colic is not considered. A thorough history and physical examination must be conducted to rule out any medical or surgical causes of infant cry. Important negative history includes history of fall, fever, vomiting, seizures, poor oral acceptance, crying associated with micturition, ear discharge or vaccination. Detailed head to toe examination must be conducted. Freedman [39], in an attempt to determine the role of laboratory investigations in colic, conducted a study in which a series of laboratory investigations were ordered based on history and examination. Positive test results were obtained in 14.1% of cases but diagnosis based on this positive result was made in only 1.4% of cases. It was thus concluded that detailed history and examination are the cornerstone in diagnosis of colic. Routine use of fluorescein stain to rule out corneal abrasion and stool for occult blood is not recommended in all cases but he recommended urine examination of all afebrile infants with colic in first month of life.

There are no established guidelines for management of colic. In general, treatment is individualized with special emphasis on counseling the parents about the benign nature of the condition and addresses their sense of inadequency. The other treatment options available but less commonly used are lactase supplementation, use of probiotics, anti-spasmodics, hypo-allergic formula feed. A brief review of the treatment options available is discussed here. The treatment is devised based on the etiological theory of colic, *e.g*., lactase supplementation for lactase deficiency, probiotics supplementation in case of altered gut flora, antispasmodics for smooth muscle relaxation, counseling of the mother to learn infant soothing techniques, chiropathic techniques. Broadly these interventions are classified as parental behavioral interventions, dietary supplementation, pharmacological intervention and manipulative therapies. A Cochrane review of the pharmacological treatment and manipulative therapy is available separately [40,41]. Four more Cochrane reviews are ongoing on parent training program, dietary modification and probiotics in prevention on infantile colic and probiotics for treatment of colic [42-45].

Behavioral modification and Parental counseling: Even though much research work is done on lactase and probiotic supplementation, one should always remember that proper counseling is the basic. The behavioral cause states that altered parent child interaction can be a cause of colic. It has been proposed that misinterpretation of infant cries lead to ineffective care giver response which inturn leads to

unsatisfied infant. Behavioral modification is usually considered as a first line intervention because it is not associated with any side effect and cost effective [46]. Proper counseling includes explaining the normal crying pattern of infants, encouraging them and helping them build confidence as parents, encouraging continuing breast feeding and infant calming techniques. Techniques to calm a crying baby should be taught to parents. One such technique is the 5s technique which includes Swaddling, Side/ stomach, Shh-sound, Swinging the baby with tiny jiggly movements, Suckling (letting the baby suckle on breast/ clean pacifier). Other techniques of infant calming include use of white noise, minimal handling, and simulating car ride. Parental counseling has been shown to be more effective than dietary change (crying duration decreased from 3.2 h to 1.1 h per day in counseling group and from 3.2 to 2 hours per day in dietary intervention group). A recent concept is the period of "PURPLE Crying" [48]. This concept was developed by Barr to help parents understand the implication of colic and the dangers of child abuse associated with excessive crying. The word PURPLE is an acronym which stands for "Peak of crying, Unexpected, Resists soothing, Pain like faces, Long lasting, Evening". The word "period" means crying has a beginning and an end. It was suggested that explaining the pattern of crying to parents would decrease the hospital visits for excessive crying and understanding that excessive crying as a part of normal infant development would reduce maternal anxiety and infant abuse. The counseling was done in the form of a 10 page booklet and a 10 minutes DVD which was given to parents after delivery. With the implementation of the concept of PURPLE Crying the emergency room visits for excessive crying decreased by 30% over 3 years [48]. Thus counseling is the first line of therapy which can be used while awaiting infant colic to run its natural history.

Dietary Modification

Lactase supplementation: Lactase supplementation as a dietary intervention is undergoing tremendous research. But none of the studies are of high quality and outcome measures are not uniform to come at a conclusion. Kannabar, *et al.* [49] conducted a double blind placebo controlled randomized control trial with cross over with a wash out period of five days to determine the efficacy of lactase supplementation and found pre incubation of feed with lactase reduced the crying time and breath hydrogen content in the intervention group. Similarly, in a crossover randomized control trial conducted by Kearney, *et al.* [50], a reduction of mean crying duration by 1.14 hours/day in the intervention group was shown. But both these studies have several limitations, small sample size, Kannabar *et al.* [49] used a symptom duration of 2 weeks for colic, outcome measures were not standardized, cross over period was different. Even though some studies have shown the effectiveness of lactase supplementation, no strong evidence has been shown which would help in formulating guidelines. More trials in larger population groups are required which will also be helpful in formulating the guidelines.

Probiotic supplementation: The supplementation of probiotics in infants with colic is based on the etiological theory that colic is due to altered gut flora. The most researched bacteria is *Lactobacillus reuteri* DSM 17938. A recent review article analyzing three randomized control trials stated that probiotic supplementation significantly reduced the crying duration in breast fed infants [51]. All infants were given *L.reuteri* 17938 orally in a dose of $1x10^8$ cfu as five drops a day. But the limitation of these studies was a small sample size and lack of cross over data and duration of supplementation was not same and one study used *L.reuteri* 55730 strain [52–54]. Most of the studies conducted on the use of probiotics have a favorable result but in a randomized control trial conducted by Sung, *et al.* [55] involving 167 infants less than 13 weeks found that *L.reuteri* did not reduce the crying time in infants with colic. They also suggested that the improvement with the use of probiotics can be actually a part of the natural course of the condition than the actual effect. Thus more randomized control trials are required involving large sample size to produce evidence for use of probiotics. As Wreeth [26] had suggested the possible role of probiotics supplementation in infants even before the onset may prevent the development of colic, based on this a Cochrane review on the role of probiotics to prevent infantile colic is under process [44]. Another Cochrane review on the role of probiotics as a treatment option is also ongoing [45]. Thus role of probiotics in both prevention and treatment of colic needs to be evaluated. Other strains of *Lactobacillus* and *Bifidobacter* have also been used but the scientific evidence is limited.

Hydrolyzed infant formula/ infants with cow milk allergy [CMA]: Cow milk allergy can manifest as colic rarely. In infants shown to have cow milk allergy, dietary modification is recommended by ESPGHN [56]. In exclusively breast fed infants with CMA, breast feeding should be continued but all forms of milk products should be restricted from mother's diet. In a mixed fed infant with CMA, the baby should be given only breast feed and no restriction of maternal diet is required. In a formula fed infant with CMA, extensively hydrolysed formula should be considered. Soy based formulas are not recommended for infants less than 6 months [56].

Fermented formula with oligosaccharides: With the hypothesis that fermented formula along with oligosaccharides decrease the incidence of colic in infants, Vandenplas, *et al.* [57] conducted a double blind randomized control trial and found that the overall incidence of infantile colic was less in the group fed with fermented formula along with oligosaccharides (short chain galacto-oligosaccharides and long chain fructo-oligosaccharides) as compared to the group which were fed either with fermented milk or oligosaccharides alone. More research is needed on the use of fermented formula with oligosaccharides.

Pharmacological intervention

The various drugs that have been used are dicyclomine hydrochloride, cimetropium bromide, simethicone, sucrose and herbal medications. These are mainly used as pain relieving agents. The studies

selected for the Cochrane review compared these pharmacological agents with placebo with respect to reduction in cry duration as primary outcome [40]. It was declared that Simethicone had no role in decreasing the symptoms of colic. Herbal medications decreased the symptoms of colic but were associated with side effects. The drugs dicyclomine and cimetropium are used in colic based on the etiological theory that pain in gut is due to immaturity of the enteric nervous system which leads to spasm in intestine. Dicyclomine and cimetropium are smooth muscle relaxants which act on the cholinergic and muscarinic receptors respectively and cause smooth muscle relaxation. Use of dicyclomine is associated with side effects like breathing difficulty. Therefore, it is not routinely used in children less than 6 months. Other agents like cimetropium, dicyclomine, sucrose had very low quality evidence for use in colic. Thus it was concluded that no recommendation could be made on the effectiveness of pain relieving agents for treatment of colic [40]. Use of gripe water is common in this part of the world. In a study conducted in JIPMER on 335 mothers of infant aged 1-6 months showed that 64.28% of mothers used gripe water and their most common belief was that it aided in digestion and decreased abdominal pain [58]. Present day gripe water are alcohol free but its use in infants is not recommended as there are no proven health benefits and use of any pre lacteal feed in infants is not recommended by WHO. Presumptive diagnosis of GERD in excessively crying infants and use of proton pump inhibitor is not recommended by NASPGHAN (North American Society for Pediatric Gastroenterology, Hepatology and Nutrition) and ESPGHN (European Society for Pediatric Gastroenterology, Hepatology and Nutrition) [59]. If a strong possibility of GERD is kept, then proper referral and investigations should be done before starting any acid suppression medication.

The other less commonly used techniques are chiropractic manipulation. In a Cochrane review on manipulative therapy, no definite recommendations were made on its use even though RCTs have shown its effect [41]. This was because the poor study design and risk of bias in those studies.

Consequences

Infant colic is a benign condition which improves with time. There are usually no associated abnormality and long term sequelae in both baby and mother [25]. Despite its benign nature it can act as a significant stressor for parents which leads to self-doubt, premature termination of breast feeding or even child abuse. Long term consequences though few have been documented in literature include recurrent abdominal pain, behavioral problem, eating problem and migraine.

CONCLUSION

Infant colic is a condition of multi-factorial etiology with wide variety of treatment options. The diagnosis of infant colic is entirely clinical and laboratory investigations are not recommended. Even after the diagnosis of colic, the child should be properly followed-up. At a time when most of the research is being focused on infant feed supplementation, it should not be forgotten that counseling is the cornerstone of

management till high-level evidence regarding other treatment options is available. Even though there is insufficient evidence regarding the effective treatment options for infant colic, few commonly used options have been rejected based on current evidence like Simethicone, Dicyclomine, Proton-pump inhibitors, and Gripe water. Dietary modifications like lactase and probiotic supplementation have shown benefits but more randomized control trials will be required. More research is needed in this field with uniformity in definition, large sample size, different population, and uniform outcome measures.

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TABLE I MAJOR DIFFERENCES BETWEEN ROME III AND ROME IV CRITERIA FOR INFANTILE COLIC

CRITERIA	ROME III	ROME IV
Age limit range for diagnosis	Birth to 4 mo	5 mo
Main focus for diagnosis	Relied mainly on duration of crying (atleast 3 h/d for atleast 3 d/wk for atleast 1 wk).	Crying/fussing which cause distress to parents
Additional criteria for research	Separate criteria not given.	Additional criteria given which include subjective parental reporting of crying more than 3 h/d for atleast 3 d/wk and objective record by a 24 h hour cry- record dairy.

TABLE II PREVALANCE OF INFANTILE COLIC

Study	Study design	Definition(s) used	Age	Occurrence
Canivet, *et al.*, Sweden, 1996 [8]	Prospective	3h/3d/3 wk 3h/3d 1h/4d/1 wk Problem crying	0-3 mo	5% 11% 17% 3%
Canivet, *et al.*, Sweden, 1996 [8]	Retrospective	3H/3D/3W 1H/4D/1W Problem crying	0-3 mo	12% 15% 12%
Hogdal, *et al.* Denmark, 1991 [9]	Prospective	1.5H/6D/1W	0-6 mo	19%
Van tilburg, *et al.,* California, 2015 [10]	Questionnare	ROME III	0-4 mo	5.9%
Hide, *et al.,* Wales, 1982 [12]	Prospective	Mothers interpretation as colic	0-12 mo	16%
Vanderwall, *et al.*, Netherland, 1998 [13]	Retrospective	>3H/1D Crying a lot Difficulty to comfort	2-3 mo	7.6% 14% 10.3%
Talachian, *et al.* Iran, 2008 [14]	Prospective	3H/3D/3W	0-3 mo	20%
Chogle, *et al.*, Colombia,2016 [15]	Prospective	ROME III	1-4 mo	27%
Rubin, *et al.*, Norwich, 1984 [16]	Prospective	Unexplained crying	0-3 mo	26%

h=Hours, d=Days, wk =Weeks