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Pathophysiology of Infantile Colic and Current Treatment Options

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Abstract
The etio-pathogenesis of infantile colic, benign self-limiting condition, is inconclusive with myriad theories abound. Infantile colic is said to be an early expression of childhood functional gastrointestinal disorders. Colic is a diagnosis of exclusion after a detailed history and physical examination have ruled out concerning causes. Alterations in fecal microflora, intolerance to cow's milk protein or lactose, gastrointestinal immaturity or inflammation, increased serotonin secretion, poor feeding technique, and maternal smoking or nicotine replacement therapy have been implicated. A pathophysiological approach to the treatment of infantile colic along with duration-based algorithms, will help in deciding management. Parental reassurance and Probiotic supplementation with Lactobacillus reuteri DSM 17938 are key components for the management of colic

Keywords:*infantile colic, gut microflora, gastrointestinal, L.reuteri DSM17938*

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I. Introduction

Infantile colic, a syndrome characterized by paroxysmal and inconsolable crying, accounts for 10–20% of pediatrician visits [1]. The crying typically starts in the first few weeks of life and ends by 4 to 5 months of age [2]. The diagnosis of infantile colic relies on the symptom-based Rome IV criteria, which is adapted from the "Rule of Three" originally proposed by Wessel et al.: 3 hours per day, ≥3 days per week, ≥3 weeks [3]. Understanding the pathogenesis of infantile colic is of prime importance in appropriately targeting the root cause or trigger and deciding the overall management.

Multiple prenatal and postnatal theories have been proposed to explain the pathogenesis of infantile colic; however a single theory independently is not absolute and can't justify the complexity of problem. Some of the common theories are maternal smoking & migraine, gastrointestinal immaturity, visceral hypersensitivity, altered gut hormones and fecal micro flora, intestinal inflammation etc. Choosing one approach often means placing weight on some aspects at the expense of others. Combining these theories into a cohesive understanding has historically been challenging.

Limited published literature suggests various combinations of these theories. Further, in their attempt to treat infantile colic with its complexities and problems, physicians often recognize the inadequacy of therapeutic measures. This comprehensive review compiles and discusses the various theories, and their evidences along with its relevance to available treatment options.

II. Methods

Literature search

A thorough literature search was conducted with key words infantile colic, functional GI disorders across databases such as medline, pubmed, google scholar with no timeline restrictionsupto December 2019.

Ethical Approval:

The approval of ethical committee is not obtained as this is a review of literature and does not involve any participants

Infantile colic: Pathophysiology spectrum

Infantile colic is not a single pathophysiological entity and appears to have a complex etiology. Multiple prenatal and postnatal factors act together to create a spectrum of pathogenesis. Prenatal factors include maternal education, smoking habits, domestic violence and maternal distress in pregnancy while gastrointestinal, psychosocial, and neurodevelopmental disorders have been suggested as three major postnatal causes of colic (figure 1).

Post-natal Factors

1. Gastrointestinal disorders

Altered intestinalflora

Lower microbiota diversity and stability in the first weeks of life may lead to changes in the metabolome of gut microbiota, the ensemble of gut microbiota by-products which influence human health [4,5]. Changes in bacterial metabolome may influence gut motor function and gas production which subsequently contributes to occurrence of colic [6]. Additionally, a less diverse gut microbiota has been associated with higher levels of calprotectin, a known biomarker of gut inflammation [7].

Culturing studies revealed higher counts of *Escherichia, Klebsiella, Serratia, Vibrio, Yersinia,* and *Pseudomonas* in the feces of colicky infants compared with healthy infants [6,8]. Even *Helicobacter pylori* infection has been implicated in colic. A case control study found that colicky infants (n=55) were more likely than those without colic to have *Helicobacter pylori* antigen in their stool (odds ratio, 15.3 [95% CI, 17.9-29.8]) [8]

Oral supplementation of probiotics, especially *L. reuteri* DSM 17938,has been shown to improve the symptoms and decrease the duration of crying [9, 10, 11, 12, 13]. This protective effect might be related with the fact that Lactobacillus are able to induce the expression of anti-inflammatory genes [14], improving gut function and motility and exerting a reduction of visceral pain [15,16]

Altered Intestinalmotility

Gastrointestinal peristalsis is controlled by a complex neuronal network, the enteric nervous system (ENS). Transient dysregulation of this nervous system during development may cause hyperperistalsis in infants with colic, particularly during the first few weeks of life [17,18,19]. A prospective study conducted by Oshikoya et al found that abdominal cramps with hyper-peristalsis (39.8%) were the most frequently correct cause of colic identified by mothers [20].

Hormones

At birth, babies have high levels of progesterone, which helps relax the muscle of the intestine. The progesterone levels drop after one to two weeks and may account for increase in colic symptoms at that time. Basal motilin levels have been shown to be elevated in colicky infants independent of their diet and are higher at birth in infants who later develop colic [21]. Motilin is a 22 amino acid hormone that promotes small bowel peristalsis and leads to faster gastric emptying, causing intestinal pain [22]. In addition, infants with colic-like behavior also have higher level of ghrelin (the hunger hormone) as supported by Savino et al study, showing higher levels of serum ghrelin and motilin (2534.2+/-600.0 pg/ml and 94.6 ± 23.2 pmol/l) in colicky infants as compared to controls (2126.1+/-281.3g/ml; p=0.011 and 64.1 ± 30.1 pmol/l; p=0.001) [23]. In another study random urinary concentrations of 5-hydroxy-3-indole acetic acid (5- OH IAA), a serotonin metabolite, were measured in infants with and without colic. 5-OH IAA levels were found to be higher in colicky infants than those in the control group [24]

Lactoseintolerance

In infants, a variable proportion of dietary lactose is not absorbed in the small bowel and arrives in the colon where it undergoes bacterial fermentation. The products of this fermentation are hydrogen and lactic acid where the latter induces osmotic pressure, favoring the influx of water, causing gut distension. The hydrogen gas also distends the colon and results in pain. [25]. This gas is excreted in the breath and can be measured, as an index of incomplete lactose absorption. Astudy conducted by Miller et al found 29 ppm breath hydrogen levels in about 62% of colicky infants than 11 ppm in 32% of control [26]. The only possible treatment for lactose intolerance in bottle-fed infants was the avoidance of lactose- containing dairy products. A double-blind randomized placebo-controlled crossover study in 53 colicky infants had found a modest benefit of pre-incubation of feeds with lactase on colic symptomsandstatisticallysignificantlowerbreathhydrogen($P < 0.0001$) [27]. However, the difference in the breath hydrogen levels between the colicky and control group could depend on other factors like the nature of the bowel flora, colonic bacterial metabolic pathways, partial pressure of hydrogen in the colon, gut perfusion and incomplete monosaccharide absorption in the gut [26].

Immaturity of the digestivesystem

Immature GI tract in the newborn cannot readily digest and absorb all macronutrients adequately; residual proteins might enter the colon to be fermented by the locally-residing microbiota thus leading to painful GI problems [28]. de Belle et al. concluded that the ileal mechanism for active transport of bile salts is undeveloped in the fetus and newborn infant. The results suggested that loss of bile salt from the immature intestine may contribute to steatorrhea and to the "diarrhea" of newborn infants. de Belle drew attention to the analogy between immaturity of bilirubin conjugation and excretion in neonatal jaundice that resolves itself in a few days, and immaturity in bile acid production and function, that resolves in a few weeks [29]

Gastro-esophageal reflux disease (GERD)

GERD and infantile colic are two different clinical conditions. However, the confusion arises when GERD does not show its typical symptoms but is rather only characterized by excessive crying, similar to colicky infants. Thus, particular care must be taken in the differential diagnosis of these twoconditions. The cause effect relationship of infantile colic and GERD remains to be further explored

In a study of 26 colicky infants with persistent, excessive crying of more than 4 weeks duration, Berkowitz and colleagues detected pathologic GERD in 61% (16/23) of the infants using a 24-hour continuous intra-esophageal pH monitoring. Although the data appeared compelling, a cause-effect relationship could not be establishedbecauseinfantsdidnotexhibittheclassicsymptomsofGERDsuchasregurgitationand vomiting. Moreover, 12 (75%) of the 16 infants with pathologic GERD were 4 months or older, by which age infantile colic has generally resolved [30]. In 2010, Howe et al found that Infant Gastro-esophageal Reflux Questionnaire Revised (I-GERQ-R) scores [a validated survey tool, to determine the frequency and severity of GER symptoms] decreased with age[31]. Another study showed that parents of infants with suspected GERD reported significantly more crying than normal (54% vs 14%, $P < 0.001$, OR 3.9), crying for more than 1 hour per day (54% vs 17%, $P < 0.001$, OR 3.2), crying for more than 3 hours per day (28% vs 3%, $P < 0.001$, OR 9.3), or crying during or after feedings (80% vs 14%, $P < 0.001$, OR 5.7) [32].

Foodhypersensitivity

Cow's milk protein appears to be associated with significant number of cases of infantile colic. Dietary cow's milk proteins are presumed to act as antigenic stimuli of a gastrointestinal hypersensitive reaction. It occurs when mast cells are activated by antigens reacting with IgE bound to IgE receptors on the mast cell surface to trigger the release of histamine [33]. Several trials have demonstrated the benefit of extensively hydrolyzed formulas and maternal avoidance of highly allergenic foods in infants with colic. The detailed explanation of this topic is beyond the perview of this review

2. <u>Neurodevelopmental disorders</u>

Immaturity of the nervous system

Some infants have an immature nervous system, causing hypersensitivity and difficulty in regulating their response to stimuli [34]. ENS can be altered in a number of ways eg. With stress,infections, and changes in nutrition, a significant modification of the ENS occurs not only duringthe fetal period but also postnatally [35]. It is thought that due to immaturity of nervous system and the bowel, the air is trapped in the colon causing stretching of the bowel, hence the colic [21].

Excessivestimulation

Infants with a low threshold for overstimulation may respond to environmental stimulation with excessive irritability and crying. Lester, Boukydis, Garcia-Coll, and Hole (1990) proposed that dominance of the sympathetic nervous system over the parasympathetic system would explain the lower threshold for arousal and the sudden onset of crying, and also would explain an infant's apparent difficulty to inhibit a crying episode once started [36]. As the central nervous system matures and become less sensitive to external stimulation, the symptoms exhibited by colicky infants are also alleviated [37].

Alterations in circadianrhythm

The main circadian clock that governs the human biological rhythms for the timing of sleep, body temperature, feeding, and melatonin secretion is the suprachiasmatic nucleus (SCN) of the hypothalamus [38, 39, 40]. A number of authors have noted that colicky infants sleep less than infants without colic. These differences remained for nighttime (12 a.m.–8 a.m.) sleep, even when crying was controlled for, and suggested that colic might be associated with a disrupted or delayed circadian rhythm [36]. In 2010, Yalcın et al., found more frequent regular sleeping pattern in non-colic group than infantile colic group (66.2% vs. 48.9%, $P = 0.035$). Sleep duration, both in daytime and at night, was shorter in the infantile colic group than that in the non-

colic groups (4.8 vs. 6.0 h in daytime, P = 0.006; 5.7 vs. 6.8 h at night, P = 0.003) [41].

3. Psychosocial disorders

Inadequate interaction between mother and infant (infant–parentinteraction)

The occurrence of colic has been attributed to personality disorders associated with an irritable and hypersensitive infant. The mother infant, father–infant interactions have been studied and found to be less than optimal in familieswith colicky infants [42]. Saeidi et al found kangaroo care more effective than conventional care for colicky infants with about 1.8 hr/d drop in the duration of fussing/crying after 7 consecutive days of care (P<0.05) [43]. Behavioral approaches are the most accepted practice for the elimination of colic. Some approaches are cuddling the infants, swinging (rhythmic rocking), using rhythmic sounds, swaddling, decreasing stimulation of the baby and parental training. In Yilmaz et al. 2015 study, there was a bigger decrease in crying durations of the infants who belonged to the group of swinging (rhythmic rocking) in arm as compared with the infants who belonged to the group of swinging on blanket [44].

In 2010, a nested case control study found more impaired bonding cases in the infantile colic group than the non-colic group at visit 2 (21.3%, 9.9%, respectively, P = 0.042) using Postpartum Bonding Questionnaire (to assess mother–infant bonding). In addition, the Edinburgh Postnatal Depression Scale (EDPS) score was also used in this study to identify post-partum depression. The mean EDPS score of IC group at visit 2 was significantly higher than the non- colic group (10.6±5.6, 7.0±4.6, respectively, P < 0.001). The percentage of cases with pathological EPDS at visit 2 was higher in infantile colic group than non-colic group (36.2%, 10.6%, respectively, P < 0.001) [45].

Akman et al. reported that depression scores were higher and maternal insecure attachment style was greater in infants with colic than infants without colic.[46].

Difficult infanttemperament

According to Rothbart, temperament has been defined as relatively consistent, constitutionally based individual differences in reactivity and self-regulation [47]. Temperament with a strong biological component is determined to a great extent by hereditary and regulatory disorders contain an additional interactional component between child and caregiver (learning experience) [48]. It is closely related to the excitation of the central nervoussystem and is seen as a biological foundation of later personality, [49] influencing behavior, the autonomous nervous system (sympathetic and parasympathetic nervous system functions) and activation of the cortex [50]. Schwartz et al haveexplored the relation between infant temperament at 4 months of age and its effect on brain structure in adulthood. Their results suggested that regional differences in the thickness of the adult orbitofrontal and ventromedial prefrontal cerebral cortices are predicted by temperamental differences observed during the first months of life [51].

Previous research has linked excessive crying in infancy to temperamental traits such as negative emotionality or "difficult temperament" during toddlerhood [48]. Stifter and Spinrad show that excessively crying infants had higher levels of negative emotionality and a lower capacity for self-regulation at 5 and 10 months during a laboratory examination compared to "typical criers"[52]. Wurmser and colleagues reported that infants with a diagnosis of excessive crying at the age of 4 months were judged to be temperamentally more "difficult" at 30 months in comparison to other children [53]. Similarly, Desantis and colleagues found an association between duration of whining and unease in the first weeks of life, negative emotionality and externalizing disorders from 3 to 8 years of age [54].

Method offeeding

Some evidences suggest that positioning and attachment of the baby during breastfeeding may be contributory factors to the incidence of colic [22]. Akter et al. reported that incidence of colic is more in infants with disorganized feeding behaviour, less rhythmic nutritive and non-nutritive suckling, more discomfort following feeding and less responsiveness during feeding interactions [25]. Evans et al. compared the effect of two methods of breastfeeding such as prolonged emptying of one breast at each feed (n = 150) vs. both breasts equally drained at each feed (n = 152) on breast engorgement and infantile colic. The former group had a lower incidence of breast engorgement in the first week (61.4% versus 74.3%; p < 0.02) and of colic over the first 6 months (12% versus 23.4%; p < 0.02), but the majority ofmothers in this group (63%) felt it necessary to offer the second breast at the end of a feed to satisfy their infant's hunger [55]

Domesticviolence

Lee et al. identified physical violence including the shaken baby syndrome as risk factors for infantile colic. Therefore, while evaluating infantile colic, clinicians should consider the risk of child abuse and check psychological environment of infants with colic at child health supervision visits [56]. Similarly, in 2010, a nested case–control study found higher domestic violence in the infantile colic group than the non-infantile colic group (14.8% vs. 2.8%, P = 0.002) [41].

Pre-natal factors

Maternaleducation

Studies have examined the relationship between maternal education and infantile colic. A study by Yalcın et al in 2010 found maternal education ≤8 years (OR = 3.22 [95% CI 1.24, 8.36], P = 0.016) as an independent perinatal predictors of infantile colic. Instead superior maternal intelligence and higher education were found to be associated with incidences of infantile colic [41]. However, there is conflicting evidence across studies to demonstrate relationship between maternal education and infantile colic [57, 58, 59].

Smokinghabits

Prevalence of colic was twofold higher in infants of mothers who smoked 15 or more cigarettes per day during pregnancy [60]. Reijneveld et al also found nearly two-fold increased risk for "excessive crying" in infants of mothers who smoked 10 or more cigarettes per day throughout pregnancy, although effects for maternal smoking were not significant after adjustment for confounders [61]. In 2008, Canivet et al found a 1.7-fold increased risk of colic related to maternal pre as opposed to postnatal smoking [62]. A large Danish study with data from more than 60,000 infants not only corroborated the association between maternal smoking and infantile colic, but actually found thatnicotine replacement therapy also increased the risk of subsequent colic, thereby suggesting that nicotine itself may be culprit.

Maternal distress during pregnancy

Søndergaard et al. examined the association between psychosocial exposures during pregnancy and the risk of infantile colic. A diary with a record for postpartum weeks 4–8 was used to quantify the amount of the infants' crying and fussing. A threefold increased risk of infantile colic (OR = 3.7; 95% CI: 1.1–13.2) was found for mothers who reported general stress during pregnancy, and twice as likely if they reported psychological stress [60]. On the other hand, higher levels of maternal social support during pregnancy are associated with lower rates of maternal reported infant colic (adjusted odds ratio (AOR), 0.55, 95% confidence interval (CI), 0.40-0.75) [41].

Migraine

Colic has also been suggested as an early life expression of migraine. A recently published study by Gelfand et al reports that 2-mo-old infants of mothers with a history of migraine are 2.6 times as likely to have colic than infants whose mother do not suffer from migraine [63]. The explanation for this may be strong genetic underpinning and possible relation between maternal migraine and intestinal microbiota [6]. Moreover, children with migraine are more likely to have experienced infantile colic compared with controls (OR ranging from 1.6 to 6.6 between different studies) [64, 65, 66]. These different studies indicate the existence of an association between migraine in childhood and infantilecolic.

Current treatment options for infantile colic

Infantile colic causes a lot of distress to parents and care givers; the most appropriate intervention is to address the root cause of this condition. Reassurance will go a long way in allaying parental anxieties. Probiotics such as Lactobacillus reuteri DSM 17938 have shown significant benefits in reducing crying time in colicky infants and also have the potential to address the long term consequences of infantile colic

Earlier evidences such as Garrison and Christakis (2000), in their review of studies that have investigated the effectiveness of behavioral interventions, found decreased stimulation (swaddling, placing in a dark room, "white noise") was the only behavioral treatment found to be effective. Ensuring the baby is well positioned during breastfeeding may also lead to a reduction of colic.

Parents should be encouraged to follow a cue based care; it has been shown that sleeping in the same room, skin to skin contact for 10 h a day while awake, feeding or sleeping and providing various sensory stimuli to the baby reduces crying by about 50%. But none of these practices have compelling evidences to treat the condition.

There is an increasing knowledge of the role of gut microbes as an etiological agent in the causation of infantile colic. In a study in Dutch infants, reduced diversity in bacterial species (bifidobacteria and lactobacilli) was identified in faecal samples taken from infants who went on to develop colic versus age-matched controls. Supplementation of probiotics especially *lactobacillus reuteri* ATCC 55730 and its daughter strain *Lactobacillus reuteri* DSM 17938 has been shown to have beneficial effects in breastfed infants [6]. A systematic review conducted by Bird et al evaluating the use of probiotic supplementation in infants with colic reported that supplementation with the probiotic *L reuteri*, administered at a dose of 10^8 CFUs once daily, to breastfed infants less than 6 months of age resulted in significantly greater improvement in colic symptoms at the end of treatment (21 or 30 days) compared to controls [67. Based upon analysis from six studies,

Abrahamsson and his colleagues summarized about 55.9 min/day reduction in crying duration among infants supplemented with L reuteri as compared to placebo [68]. A recent meta-analysis by Sung et al underlines that *L. reuteri DSM 17938 is an* effective option for treatment for crying in exclusively breastfed infants with colic [69]. One study by Indrio F et al for prevention of infantile colic and other functional gastrointestinal disorders with supplementation of L.reuteri DSM 17938 has demonstrated positive results in reduction of crying time, reduced number of regurgitation episodes and increased evacuations compared to placebo.[70]

Bottle fed infants with colic may additionally benefit from the exclusion of cow's milk and lactose

milk. By avoiding other potential allergens like egg, peanuts and wheat also, it may be possible to decrease the occurrence of infantile colic.The American Academy of Pediatrics' Committee on Nutrition does not recommend changing to soy formula in themanagementofcolic. According to ESPGHANguidelines,soymilkisnotindicatedforusein infants below the age of 6 months, and hence has no role in the treatment of infantile colic. The use of anti-cholinergics like atropine,

Hyoscine and dicyclomine decrease the intestinal spasms and may produce relief from colic. However, the adverse effects including identified breathing difficulties, seizures, and asphyxia are noted. Dicyclomine is contraindicated for infants younger than 6 months. Simethicone, a defoaming agent, has also been studied as colic reliever, but has not been shown to provide beneficial results

Herbal supplements, including zingiber, cumin, cardamom, ginger, fennel, black pepper and various herbal teas (including fennel, chamomile, vervain, lemon balm, and licorice) may help calming the infant and reducing abdominal distension. However, the administration of herbal products in infants with colic raises some concerns about the potential nutritional effects (these treatments provided for a long time could lead to a decreased intake of milk), the lack of standard dosages and the possible content of sugar and alcohol. In conclusion, parents have to use them with attention and under medical control.

A 2016 Cochrane review concluded that the effectiveness of pain-relieving agents in treatment ofinfantile colic is sparse and the available literature had serious limitations. Simethicone, herbalagents, sugar, dicyclomine and cimetropium bromide cannot be recommended for infants withcolic[71]. Consequently, to date there is no drug that significantly alleviates colic without potentiallydangerous side effects, and this remains so.

To conclude, infantile colic is often a stressful problem for parents and a challenge to parenthood. Understanding the pathogenesis and need based management approach is usually more successful. Benign and self-limiting nature of this condition should be emphasized to the parents.Based on the available evidence, probiotic Lactobacillus reuteri DSM 17938 seems to be an effectivetherapeutic option considering the multifactorial etiology of infantile colic as it addresses the causeof the condition.

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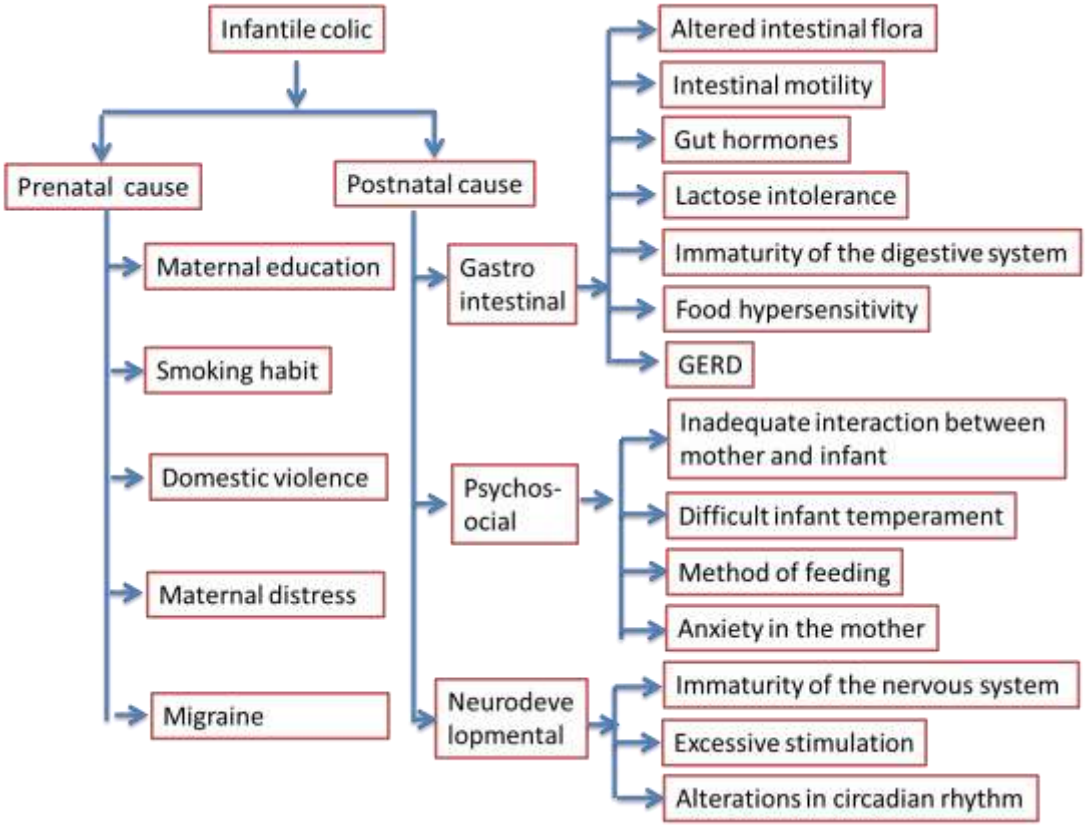
Figure 1. Multifactorial etio-pathogenesis of infantile colic



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