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Excessive crying and gastro-oesophageal reflux disease in infants: misalignment of biology and culture

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Summary Excessive crying is the most common problem presenting to the doctor in the first months of life in western industrialised societies, affecting up to 30% of infants. There has been an exponential increase in the diagnosis of gastro-oesophageal reflux disease (GORD) in babies who cry excessively over the past few decades, and many parents believe their crying infant ''has reflux''. This paper proposes that culturocentric assumptions have confused interpretation of research into GORD, and re-examines the findings of GORD research from the perspective of evolutionary biology. Evolutionary biologists argue that the human infant is an exterogestate foetus for at least the first six months of life, dependent on maternal co-regulation for optimal physiological function. However, infant-care practices in western industrialised societies shifted towards an emphasis on infant autonomy at the time of the Industrial Revolution. From the perspective of evolutionary biology, a misalignment between western culture and the biological expectations of the infant developed over two million years of evolution may result in excessive crying in less adapted babies. The key biocultural factors that impact on infant distress are feeding management, parental responsiveness, sensory nourishment and sleep management. When the concept of the human infant as an exterogestate foetus is integrated with the findings of GORD research, a hypothesis and its corollary emerge. This hypothesis proposes that infant GORD is a physiological manifestation of misalignment between biology and culture, and proposes, as a corollary, that if the impact of biocultural factors upon the physiology of otherwise well crying babies is not addressed in the first months of life, populations of infants who cry excessively may be predisposed to GORD after three to four months of age. If this hypothesis is correct, an integrated clinical approach to crying babies less than three to four months of age that considers feeding management (e.g., frequent feeds, breast- or bottle-feeding technique, referral to a lactation consultant, cow's milk allergy), parental responsiveness (e.g., prompt response to infant cues), sensory nourishment (e.g., sling or backpack, walks, massage) and sleep management (e.g., nocturnal co-sleeping) should, firstly, decrease crying when applied to infants less than three to four months of age, and secondly, decrease the incidence of GORD in these infants once they are older than three to four months of age. Thirdly, if this hypothesis is correct, combining the integrated approach with pharmaceutical intervention should improve outcomes in infants diagnosed with GORD.

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Introduction

The exterogestate foetus and excessive crying

''Evolutionary medicine takes the view that many contemporary social, psychological, and physical ills are related to incompatibility between the lifestyles and environments in which humans currently live and the conditions under which human biology evolved.'' [1]

Hominids evolved the specific narrowing of pelvic architecture necessary for bipedal locomotion about 3.6 million years ago. Between 1.5 million and 500 000 years ago the brain-size of the adult hominid quadrupled to become, proportionally, the largest of any primate. Sp. *homosapiens* evolved into the most neurologically immature of any mammal at birth because of the evolutionary need to pass such a massive brain through a bipedal pelvis [2].

Exponents of evolutionary biology argue that, as a result, the human infant for at least the first six to nine months of life is most appropriately conceptualised as an exterogestate foetus [3], pointing to evidence that it was constantly carried, had unrestricted access to the breast, and co-slept with care-givers for 99% of human history [4]. Evolutionary biologists conclude that the human infant's immature physiology is designed to expect complex co-regulatory interaction with maternal physiology [5]. This concept is supported by extensive research in the field of human lactation (see literature review [6]), by research in neonatal physiology [8—10], and in kangaroo mother care (see literature review [7]) and in neonatal physiology [8—10]. However, infant care in western societies underwent a revolutionary change at the time of the Industrial Revolution to modes of care that emphasize infant autonomy (''caching'') [4].

We know that infant primates are hard-wired to signal distress when their internal state requires regulation [11,12]. The cry of the human infant has evolved as a strategy to activate parental feedback so that physiological homeostasis is restored [13,14]. Whilst human infants have been remarkably adaptive to a wide range of practices across diverse cultures and a majority adjust to western care-giving practices, crying is the most common problem presented to the doctor in the first few months of life in western society [15]. It is variously estimated, depending on definitions used, that 20% or up to 30% of babies in western societies cry excessively for no apparent reason [16,108]. Excessive crying is not adaptive, but may impair the care-givers' ability to provide effective intervention [17], may place the infant at increased risk of abuse [18,19], and, if it persists beyond the first few months of life, may be associated with hyperactivity and academic difficulties in childhood [20,109]. A baby is most usefully defined as crying excessively when the crying distresses the parents [21]. It is important to note that whilst parents commonly believe that paroxysmal screaming, drawing up the knees, atypical facial expressions, back-arching and tensing of the abdomen indicate gut pain, these behaviours are non-specific signals of distress [22].

Ronald Barr, an eminent researcher in the field of infant colic, argues that the baby who cries excessively is less able to adapt to a misalignment between western industrialised culture and two million years of evolutionary context manifest in its biology. In the words of evolutionary biology, this baby is sensitive to a ''discordance'' between the childraising practices of our society and the childraising practices of its ''environment of evolutionary adaptedness'' [23,24]. Genetic [25] or central nervous system [18] factors may modulate the adaptability or sensitivity of an infant to misalignment of biology and culture. Barr goes on to develop the hypothesis of ''transient responsivity'': that the central nervous system of infants who cry excessively regulates ''negative responsivity'' differently in the first three months of life to those who do not cry excessively [26].

Infant gastro-oesophageal reflux disease

''...Cultural ideologies, values, and the socialization experiences of medical researchers often prevent disease and human disorders from being conceptualised in evolutionary terms...'' [1]

Terminology

Although in the 1950s infant ''gastro-oesophageal reflux'' was rarely mentioned in paediatric texts, today babies who cry excessively are commonly said, by both health professionals and members of the public, to ''have reflux''. This diagnosis is responsible for a concerning proportion of referrals to paediatricians [27,28]. In order to avoid the confusion that has characterised the research literature, this paper uses terminology that distinguishes between two physiologic events, namely:

1. *gastro-oesophageal reflux (GOR)*,
2. *gastro-oesophageal reflux (GOR) with regurgitation*, or *vomiting*; and two disease states:

3. *gastro-oesophageal reflux disease (GORD)*,
4. *secondary GORD*.

Secondary GORD results from other organic pathology, and will not feature further in this discussion. Likewise, this paper considers GORD in relation to excessive crying in infancy, and does not consider GORD-related respiratory tract complications.

Gastro-oesophageal reflux

Gastro-oesophageal reflux refers to the passage of gastric contents back through the lower oesophageal sphincter into the oesophagus. This is associated with transient lower oesophageal sphincter relaxation and is most frequent postprandially in both infants and adults. Episodes of GOR are more common in infants because oesophageal peristalsis and the anatomy of the intra-abdominal oesophagus only gradually mature with postnatal age [29].

The low fat and protein and high carbohydrate composition of human milk reflects our evolutionary development as continuous feeders in constant access to the mother's body (mammals who are episodic feeders cache their young in nests as they look for food, and have milk that is high in fat and protein) [4]. For 1–2 h after a feed, when the majority of episodes of reflux in infants occur, gastric contents are buffered by the breastmilk or formula, and the resultant non-acidic refluxate is undetectable by pH probe [30,31]. Therefore, an otherwise well infant fed two hourly, or ''snacking'' more frequently, is not susceptible to acidic GOR. An infant with interdigestive periods longer than 2 h is susceptible to acidic GOR because gastric acid secretion in fasting healthy term infants is substantial [32] and unopposed from 2 h postprandially.

We can conclude from an evolutionary perspective that excessive lower oesophageal acidification is a physiological consequence of prolonged feeding intervals in an organism designed to expect short feeding intervals (2 h or less). That is, frequent lower oesophageal acidification can be understood as a physiological manifestation of misalignment between culture and biology.

Vomiting (GOR with regurgitation)

Many health professionals and members of the public are concerned that a baby who cries and vomits frequently must ''have reflux'', though there is no evidence to support this belief in infants less than three to four months of age.

In a vomit, gastric refluxate travels beyond the upper oesophagus into the mouth. (Because an episode of GOR and a vomit are indistinguishable from the point of view of the lower oesophageal mucosa, the terms vomiting and regurgitation are used interchangeably in this discussion [33].) GOR with regurgitation occurs in up to half of normal infants from as early as the newborn period from several times an hour to several times weekly, peaking at four months when up to two-thirds of babies vomit at least once daily [34,35]. Once organic pathology such as pyloric stenosis has been excluded, the distinction between ''projectile vomits'' and effortless ''spills'' is not significant in infants who cry excessively, despite the prevalent belief that projectile vomiting is a sign of ''reflux''. Those who vomit more frequently and with greater force have increased autonomic nervous system activity, which is a variant of normal [36]. A well baby given free access to the breast may suckle out of need for sensory nourishment (oral stimulation and comfort) beyond its immediate need for nutrients, and since raised intragastric volume precipitates regurgitation [37], we can conclude from an evolutionary perspective that vomiting is one of the exterogestate foetus's self-regulatory mechanisms.

Importantly, however, infants who vomit but are not fed frequently due to the prolonged breastfeeding intervals of western culture will be prone to lower oesophageal acidification since there is less residual milk in the stomach to buffer gastric acids [38].

Assumptions underlying infant GORD research

Callahan proposes that the exponential increase in the rate of GORD diagnosis over the past few decades may be explained by three concomitant factors. Firstly, it is likely that there has been an increased rate of diagnosis because of technological advance and improved vigilance. Secondly, it is possible that there has been a real increase in the incidence of GORD due to an increase in specific childcare practices in our culture already identified as contributing to predisposition for GORD, for example, formula feeding, or positioning babies in seating devices whilst truncal tone is poor. Thirdly, it is likely that there is widespread overdiagnosis of GORD, due to the confusion about what constitutes GORD both in the medical profession and the general public [39].

It is widely agreed that the erosions and ulcerations of macroscopically visible oesophagitis on endoscopy constitute gastro-oesophageal reflux disease, and cause pain and excessive crying in the infant. The significance of a continuum of histological changes on mucosal biopsy remain less certain [40,41]. For many years a range of

other signs have been attributed to infant GORD in the medical literature, including excessive crying, vomiting, feeding refusal, backarching, failure to thrive and sleep disturbance. However, it is now accepted that none of these signs consistently relate with GORD in the infant under three to four months of age. In the infant older than three to four months, only haematemesis and respiratory complications are consistently associated with GORD [42—45].

I suggest that the confusion about GORD in the medical literature and the broader community has arisen out of two assumptions that commonly underpin medical research:

1. A symptom must result from a primary disease state.
2. The cultural practices of western industrialised society are biologically normative.

Assumption 1. ''GORD is a primary idiopathic disease entity''.

Because of the assumption that a cluster of signs loosely designated as infant GORD must comprise a primary idopathic disease entity, research into GORD throughout the 1980s and 1990s did not take into account the range of biocultural variables that affect a physiological event, or a symptom, and failed to distinguish between modifiable physiological events and a disease state.

Intra-oesophageal pH monitoring. Until recently, 24-h intraoesophageal pH monitoring was viewed as the ''gold standard'' in GORD diagnosis. This investigation quantifies the extent of lower oesophageal acid exposure in a day of observation. (Intraluminal impedance techniques are required to measure the frequency and duration of GOR [46].) However, the frequency, duration and noxiousness of GOR are affected by a complex range of variables, including timing of and composition of feeds. Whilst the intra-oesophageal pH may be less than 4 for as much as 11.7% of the day (reflux index of 11.7%) in well infants [47], the significance of the variable impact of culturally specific child-care practices on the reflux index has only just begun to be addressed. Intraoesophageal pH monitoring and intraluminal impedance manometry assess frequency and noxiousness of GOR which predisposes for GORD, but do not confirm a disease state, as a baby may be predisposed to oesophagitis without yet having sustained histological or gross lower oesophageal mucosal injury [48,49]. The research literature, using these two tools, has confused quantification of physiological predisposition with confirmation of a disease state.

Visceral hyperalgesia. In the absence of evidence linking GORD with crying in the infant under three months, despite its widespread diagnosis in this age-group, the theory of visceral hyperalgesia has come to the fore. Proponents argue that infants lack effective pain inhibitory processes and suggest that some infants learn to interpret an uncomfortable (or ''discrepant'' [50]) event, e.g., oesophageal distension, as pain. Significantly, the hypothesized treatment for visceral hyperalgesia is ''sensory overloading'' of the projection interneurons in the dorsal horn of the spinal cord, e.g., with infant massage [51].

The concept of visceral hyperalgesia is usefully re-examined from an evolutionary perspective. Humans carried their young for 99% of their evolutionary history because the exterogestate foetus, unlike other infant primates, lacks the neurological development required to cling to the mother after birth. In contrast, the average western infant has physical contact with a care-giver for less than a quarter of the day, and receives vestibular stimulation for about an hour and half an hour each day [4,52]. It has been argued that a diversity of vestibular stimulation significantly improves an infant's motor development and ability to learn [53—55], and that the more an infant's brain is showered with sensory input, the more likely it is to reach the upper limits of intellectual potential [56]. There is evidence that babies who are carried for 3 h daily cry 43% less [57], and that auditory, tactile, visual and vestibular intervention reduces the length of hospitalisation in preterm infants [58]. Nevertheless, we have not considered that the hunger for sensory nourishment (e.g., diverse vestibular, touch, proprioceptive and visual input) is biologically driven and may cause distress in an infant comparable to the distress of hunger for food, resulting in excessive crying.

I propose that the infant's capacity to integrate a discrepant event without signalling distress decreases when the infant's biological expectations for rich sensory nourishment, or ''sensory overload'', are not being met. Pain is only one of a range of experiences that cause infants to scream paroxysmally [59]. A discrepant event alone, in the absence ''sensory overload'', may overwhelm an infant and precipitate distress. From the perspective of Barr's ''transient responsivity'' hypothesis, sensory nourishment (e.g., massage [51,110], sucrose tastant [60], frequent carrying and frequent feeds [57,61]) may impact on the regulatory component of an infant's response systems, damp-

ening negative responsivity to discrepant events. From the perspective of evolutionary biology, certain infants subjected to the sensory under-nourishment relative to biological expectation that is characteristic of western infant-care practices may regularly respond to discrepant events with distress.

Assumption 2. ''Western infant-care practices are biologically normative''.

Evolutionary biology argues that the normative physiological state for the human exterogestate foetus occurs in the context of the carer's body and mother's breasts. Much research into GORD is confused by the assumption that the physiology of an infant in the absence of co-regulation by the care-giver's body (i.e., the ''cached'' baby), or an infant receiving breastmilk substitutes in part or wholly, can be viewed as biologically normative. Therefore the impact of biocultural variables has not been identified or controlled for in GORD research.

Hypothesis: infant GORD results from misalignment of biology and culture

''The doctors of the future will find it necessary to take account of the biological imperatives that Darwin revealed if they are to have any real understanding of their trade as it will be practised in the new millennium.'' [62]

Mechanisms of increased frequency and noxiousness of GOR

Fig. 1 details mechanisms that either increase the frequency of GOR or the noxiousness of GOR (see literature reviews [29,33,63–66]). If chronicity of exposure to noxious refluxate predisposes the infant to the histological and then gross mucosal changes of GORD after three to four months of life [33,42], we can hypothesise that child-care practices that increase frequency of GOR or increase the noxiousness of GOR are likely to have a gradual and cumulatively harmful effect on lower oesophageal mucosa, predisposing that infant to GORD. This occurs either by direct impact on the physiological mechanisms of GOR, or by causing excessive crying which impacts on the physiological mechanisms of GOR.

Excessive crying affects frequency and noxiousness of GOR

We know that stress or excitement (i.e., autonomic nervous system arousal) affects gastrointestinal function and symptoms in adults [67,68]. I propose that there are three ways in which infant distress may increase frequency and noxiousness of GOR. Firstly, babies who cry excessively are likely to have higher levels of autonomic nervous system arousal, with associated oesophageal dysmotility, incoordinate gastric contractility and delayed gastric emptying [36,67,69]. Secondly, a temporal association between crying and GOR episodes with or without vomiting occurs, due to the mechanical

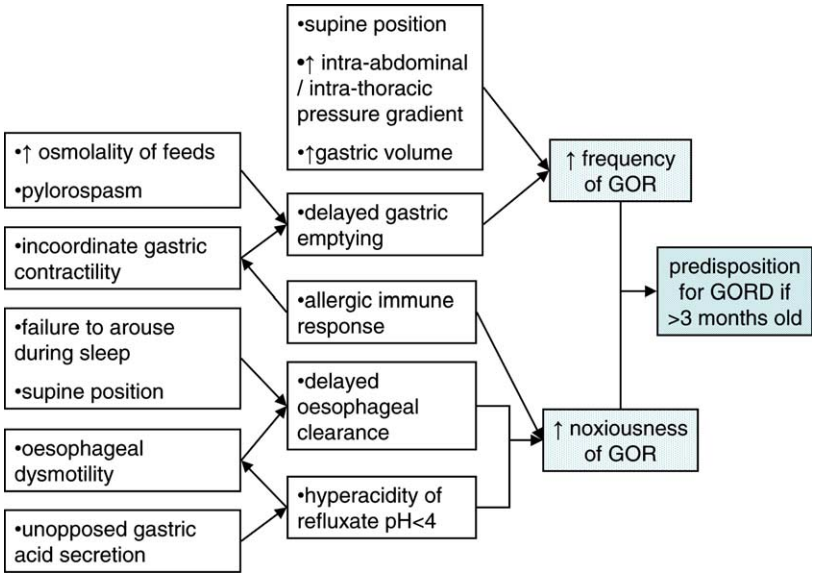

Figure 1 Mechanisms of predisposition for gastro-oesophageal reflux disease.

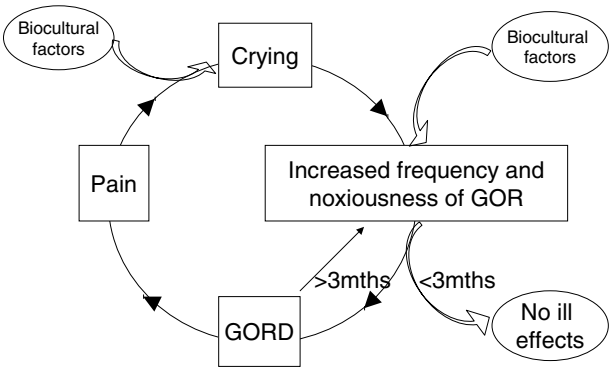

Figure 2 Crying and the gastro-oesophageal reflux disease cycle.

effects of raised intra-abdominal pressure from forced expiratory strain, and decreased intra-thoracic pressure from deep inspiration [29,70,71]. Thirdly, babies too distressed to feed during bouts of prolonged crying are at risk of refluxing unopposed gastric acid secretion. I hypothesize, therefore, that certain biocultural factors associated with excessive crying in the infant are likely to increase frequency of reflux and its potential noxiousness; and that populations of infants who cry excessively do not show ill effects in the first three months, but beyond that may be predisposed to GORD because of the chronic effects of frequent crying on mechanisms of predisposition for GORD (Fig. 2).

Biocultural factors affect frequency and noxiousness of GOR

Integration of research in the fields of excessive crying in infancy, human lactation and evolutionary biology leads me to consider four key biocultural factors that impact on infant physiology: feeding management, parental responsiveness, sensory nourishment and sleep management. This section examines the proposition that each biocultural factor impacts on:

1. excessive crying in infancy, and
2. frequency and noxiousness of GOR, thereby contributing to predisposition to GORD.

In order to allow testing of the hypothesis that infant GORD results from a misalignment of culture and biology, I have used the four key biocultural factors to formulate an integrated approach for the primary health care provider confronted with excessive crying in an infant less than six months old (Fig. 3). The primary health care provider using this method will be able to offer parents a range of options to explore, recognising that only parents know which strategies are manageable or desirable in their own unique contexts.

Feeding management. Breastfeeding difficulty. Studies cited to show that breastfeeding does not protect against excessive crying in infancy fail to control for the ubiquitous breastfeeding problems and prolonged breastfeeding intervals of industrialised societies [72,73], and may show the multicausal nature of infant distress rather than the irrelevance of feeding method. Medical researchers are not trained in lactation support [74—76], and as a result breastfeeding difficulties are not identified or controlled for in crying baby research. An infant frustrated by a breastfeeding problem may cry excessively despite adequate weight gain. This baby may regularly fail to settle at the breast before its initial signals of distress overwhelm and disorganise into the crying state which is resistant to soothing [59]. Low fat content in the breastfeed may result in a crying baby with tympanic abdomen, excess flatus and explosive, frothy, acidic stools. This may be rectified by foremilk/hindmilk management techniques, or may result from shortened feeds due to breast or nipple pain, poor attachment, poor positioning, infant oral thrush or suck problems [77]. Feeds may also be shortened due to an ill-informed, routinised approach to lactation (e.g., feeds restricted to ten minutes each breast). Dysfunctional sucking may partially frustrate an infant's capacity to breastfeed [78]. For these reasons, any breastfeeding infant who cries excessively requires prompt assessment by an International Board Certified Lactation Consultant [79,111]. Breastfeeding difficulties that cause excessive crying in infants may contribute to predisposition for GORD either by acidification of the lower oesophagus during prolonged breastfeeding intervals, or indirectly by the physiological impact of repeated bouts of prolonged crying.

Formula. Whilst the exterogestate foetus requires breastmilk for optimal physiological function in both developed and developing countries [80,81], many human infants receive breastmilk substitutes, with an associated increased risk of GORD [43,82—84]. Lactose-based breastmilk substitutes double the time of gastric emptying relative to breastmilk [63], causing prolonged gastric distention and increased frequency of GOR [83]. Formula fed infants are likely to be pulse fed with more prolonged interdigestive intervals and greater volumes per feed than breastfed infants, predisposing to increased frequency and noxiousness of GOR [37,39,84]. In formula-fed infants who develop cow's milk allergy (CMA), there is a steady decline in lower oesophageal pH over the

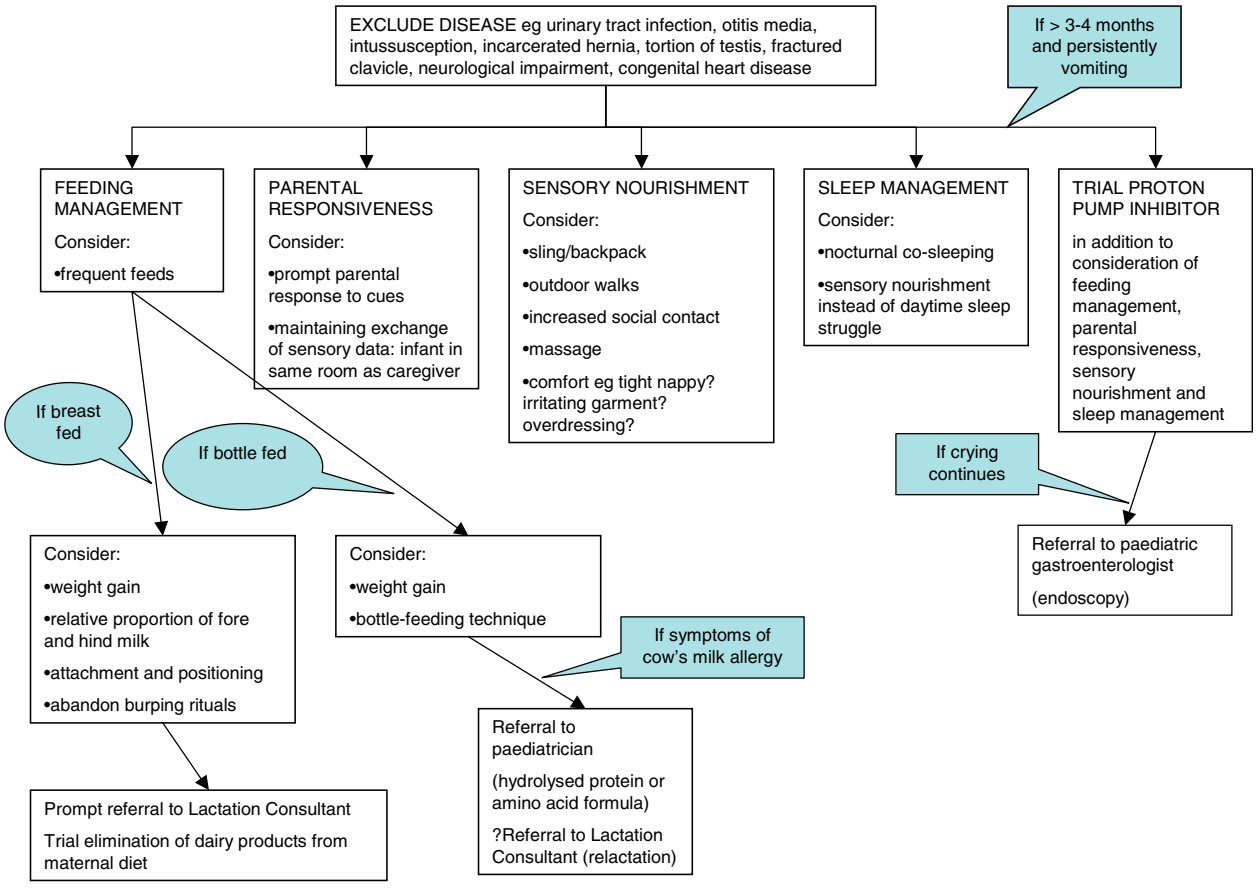

Figure 3 An integrated approach to excessive crying in the infant less than six months old.

first 2 h after a feed, further increasing predisposition to GORD [85]. A formula-fed infant diagnosed with CMA may benefit from extensively hydrolysed milk protein formula. In the 10% of infants with CMA who prove intolerant to extensively hydrolysed milk protein formula, an amino acid formula is recomended [86]. The high osmolality of both these breastmilk substitutes further increases predisposition to GORD [82]. (The deleterious tissue effects of lactose-based formulas are well documented (see literature reviews [80,87, 88]), although the short- and long-term tissue effects of amino acid-based and hydrolysed milk protein formulae are unknown.)

Allergy. Immune-mediated damage to the infant's small intestinal brush border caused by allergy to food protein (most commonly cow's milk protein) may also cause lactose overload with accompanying wind, explosive frothy stools and excessive crying [89]. There is evidence that up to 50% of GORD in infants less than one year of age is associated with CMA, either passed through the mother's milk or as a direct response to formula [85,90]. For this reason a trial elimination of dairy products from the maternal diet is indicated for breastfed infants who cry excessively [86]. The management of CMA in the infant fed lactose-based breastmilk substitutes is detailed in the section *Formula*.

Parental responsiveness. Phenomenological evidence suggests that infants who cry excessively do not cry more often, but cry for longer once started. Caretaking differences between societies in early infancy are known to affect the duration of crying rather than its frequency and pattern. Cultures in which babies do not cry for long are characterised by a prompt parental response to infant cues and cries [91,92]. There is evidence of dramatically decreased duration of crying in infants who are fed at short intervals without fear of overfeeding and who are responded to promptly without fear of spoiling [61,93]. Infants will signal with attachment promoting cries for a short period of time before becoming overwhelmed and disorganised by the crying state, which is resistant to soothing [59]. Evolutionary biologists argue that the restrained parental response promoted by western industrialised culture is another example of a misalignment

between culture and biology that results in excessive crying in infants [24]. We have previously discussed how excessive crying may impact on frequency and noxiousness of GOR, predisposing to GORD.

Sensory nourishment. The proposed relationship between sensory nourishment and infant distress has been discussed in the section *Visceral hyperalgesia*. I hypothesise that relative sensory undernourishment may contribute to predisposition for GORD by causing excessive crying, which increases frequency and noxiousness of GOR.

Sleep management. Evolutionary biologists argue that the exterogestate foetus is designed for a predominance of active sleep and associated frequent nocturnal maternal-infant arousals until it is mature enough to sleep independently and remain physiological stable [94]. This co-regulation occurs through co-sleeping, which is any sleeping arrangement that allows parent and infant close enough proximity to exchange sensory data, e.g., sleeping in the same room. (Co-sleeping is not the same as bed-sharing, but may include it.) Natural consolidation of sleep architecture occurs from about six months of age, but western childcare practices aim to condition infants into mature sleeping patterns with consolidated periods of quiet sleep much younger than this. Attempting to condition a baby into mature sleep prematurely, or not co-sleeping, may predispose an infant to GORD in three ways.

Perhaps most importantly, infants sensitive to misalignment between biology and culture may experience separation from the parent as biologically dangerous, and signal distress upon waking, which over time may predispose to GORD through the neurohormonal and mechanical effects of crying. Secondly, babies conditioned into mature sleep prematurely may be predisposed to delayed oesophageal clearance, because in quiet sleep the infant is less likely to arouse and swallow if gastric contents reflux into the oesophagus. Thirdly, babies not receiving feeds during the night are susceptible to hyperacidic refluxate [95–101].

Implications of an evolutionary approach for the management of infant GORD

Since the infant older than three months with oesophagitis will experience pain from oesophageal inflammation, erosions and ulcerations, and since oesophagitis itself causes oesophageal dysmotility and delayed oesophageal clearance [66], entrenching a pain cycle, pharmaceutical intervention is required. Proton pump inhibitors (omeprazole and lasoprazole) are widely regarded as medications of choice in the treatment of infant GORD [32,47].

Endoscopy is indicated to confirm the diagnosis if an infant older than three months of age with suspected GORD does not settle after a trial of proton pump inhibitor, for three reasons. Firstly, we know there is poor correlation between symptoms commonly attributed to GORD and GORD; secondly, there is inadequate data on the safety of prolonged gastric acid suppression in infancy [32,47], and thirdly, other diagnoses such as eosinophilic or allergic esophagitis should be excluded [90]. Indeed, any medication will yield a very high placebo response amongst infants who cry excessively [102].

Because, almost half the cases of GORD in infants less than one year of age are associated with an immune response to cow's milk protein, a trial elimination of dairy products from the diet of breastfeeding mothers is advisable [85,103]. Thickened feeds, though commonly recommended, can lead to reflux episodes of prolonged duration, and may increase the risk of oesophageal and pulmonary complications even though overt vomiting decreases [82]. The supine sleeping position continues to be recommended for infants with GORD, because the stabilised left lateral position is difficult to maintain [104]. There is no evidence to support the efficacy of the popular strategy of elevating the head of the cot by 30° [105,106].

If the hypothesis that biocultural factors impact on the pathogenesis of GORD is correct, suggesting to parents infant-care strategies that may more closely align with the evolutionary expectations of the infant will prove to be important, e.g., appropriate feeding advice; prompt parental response; increased sensory nourishment (use of carrying devices such as slings and backpacks, infant massage, outdoor walks); and co-sleeping. It is important to emphasize again that only parents know which strategies are manageable in their own unique contexts.

Importantly, an evolutionary approach to feeding management recommends that mothers allow babies with GORD to feed frequently, despite popular advice to space out feeds in these infants, since we have seen that the more frequently an infant is fed, the less susceptible she is to acid reflux. Also contrary to popular advice, an evolutionary approach recommends that mothers should not be told to offer ''short'' feeds to infants with GORD, since babies self-regulate at the breast (see literature review ''Feeding on demand'' [107]). There is no rationale for the popular advice to hold the infant with GORD who is fed breastmilk or formula upright after feeds, as neither causes acidic post-

prandial refluxate (an exception occurs with CMA to lactose-based formulas, as discussed).

Corollary hypothesis: overdiagnosis of GORD predisposes to GORD in infancy

We are already aware that inappropriate diagnosis with subsequent pharmaceutical intervention risks creating a ''special'' child with predisposition to long-term behaviour concerns [102]. Inappropriate diagnosis of GORD in infants under three months of age who cry excessively may result not only in unnecessary pharmaceutical intervention, but an associated failure to explore biocultural causes of infant distress.

If application of the integrated approach results in decreased crying in populations of infants as predicted, we would expect these same populations to have a decreased incidence of GORD beyond three months of age. The worst outcome of overdiagnosis of GORD in infants under three months of age could be that it becomes a self-fulfilling prophecy, because of the failure to consider biocultural factors once disease is diagnosed.

Conclusion

''...the application of Darwinian principles to the practice of medicine has slipped through the intellectual net of medical education, and it has been left to the evolutionary biologists to point out the need to take natural selection into account in an increasing number of fields of medical practice.'' [62]

Both health professionals and researchers have tended to apply a number of discrete strategies to the complex issue of infant distress. An integrated approach is required.

Certainly over the past few decades there has been an exponential increase in the diagnosis of GORD in babies who cry excessively, but culturocentric assumptions have confused interpretation of research into this disease. When the evolutionary biologist's conceptualisation of the human infant as an exterogestate foetus is integrated with the findings of GORD research, a hypothesis and its corollary emerge. This hypothesis proposes that GORD is a physiological manifestation of misalignment between biology and culture, and proposes, as a corollary, that if the impact of biocultural factors upon the physiology of otherwise well crying babies is not addressed in the first months of life, infants who cry excessively may be predisposed to GORD after three months of age.

Research is required to test the following: (1) Does an integrated approach drawn from our knowledge of the impact of biocultural factors on infant physiology (see Fig. 3), (a) applied as prevention, and (b) applied as intervention, decrease crying in the first months of life? (2) Does application of this integrated approach cause a decrease in the incidence of GORD after three months of life? (3) Does application of this integrated approach to infants diagnosed with GORD improve outcomes?

If this hypothesis is correct, an integrated approach to infants who cry excessively has the potential to decrease both infant distress and the incidence of infant GORD, and to improve the satisfaction of large numbers of families in those important first months of their baby's life.

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