

<sup>๕a</sup> Prevalence and Natural Course of Gastroesophageal Reflux, <sup>๕b</sup> A One-Year Cohort Study



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**Original article :**

245<sup>๕๖</sup> Prevalence and Natural Course of Gastroesophageal Reflux, <sup>๕๖</sup> A One-Year Cohort

Study in Thai Infants



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Running title - Prevalence and natural course of gastroesophageal reflux in infants

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## ABSTRACT

**Background :** Epidemiological studies in adults suggest that the nature of gastroesophageal reflux may be different among various ethnic groups. Until recently, there has been limited information concerning the epidemiology of gastroesophageal reflux in non-Western children. The objectives of this cohort study were to investigate the prevalence of gastroesophageal reflux in Thai infants and to describe the clinical course of reflux regurgitation during the first year of life.

**Methods :** A cohort study was carried out in 216 healthy neonates who attended the well-baby clinic of Songklanagarind Hospital between March-June 1998. All neonates were followed up, at regular well-baby clinic visits, for one year for reflux symptoms and clinical progress. Information concerning gastroesophageal reflux symptoms was obtained by interviewing the parents and from their diary records. An infant who regurgitated at least one day per week was considered to have gastroesophageal reflux.

**Results :** Of 145 infants who had completed a one-year cohort, the prevalence of gastroesophageal reflux peaked at 2 months with 86.9% and significantly decreased to 69.7%, 45.5% and 22.8% between 4, 6 and 8 months, respectively. At one year of age, only 7.6% of infants still had reflux regurgitation. Most Thai infants with gastroesophageal reflux had mild symptoms : 90% of them regurgitated only 1-3 times per day and daily regurgitation was reported in a low percentage. There was no significant difference in prevalence of gastroesophageal reflux between breast-fed and bottle-fed infants. Comparing between infants with gastroesophageal reflux and those without, the standard deviation scores of body weight for age were similar. No pathologic gastroesophageal reflux was observed during this study period.

**Conclusions :** The nature of gastroesophageal reflux in Thai infants differs from that of Western infants. The prevalence of gastroesophageal reflux in Thai infants was very high in the period of 1-2 months of age, however, many infants became symptom-free by 6 months. The type of feeding (breast milk vs bottle milk) had no influence on the prevalence of gastroesophageal reflux.

## INTRODUCTION

Although regurgitation from gastroesophageal reflux (GER) is a common problem in infants, the epidemiology of the condition remains a neglected field. Until recently, data regarding the natural course of GER during infancy has been very limited, and particularly no such information in non-Western infants is available.

Epidemiological studies in adults suggest that the nature of GER may be different among various ethnic groups<sup>1</sup>. According to a cross-sectional survey for gastrointestinal symptoms among an Asian population, reflux-type symptoms were reported by only 1.6% of the general population<sup>2</sup>, much smaller than Western reports of 19.8-32.6% of the population experiencing frequent heartburn at least once in the previous three months<sup>3,4</sup>. Moreover, in a well-designed study comparing the prevalences of reflux esophagitis between English and Singaporean patients who presented with dyspepsia, Kang et al demonstrated that reflux esophagitis was significantly more common in English dyspeptic patients (25%) than in Singaporean patients (4%)<sup>5</sup>. From this evidence, it seems that disorders related to GER are the diseases of the West. We believe that the influence of racial factors on the nature of GER which has been observed in adults may also be evident in children.

Since there has been no information concerning the nature of GER symptoms in non-Western infants, this cohort study in Thai infants was undertaken with two objectives : 1) to investigate the prevalence of GER in Thai infants and determine the effect of type of milk fed on the prevalence, and 2) to describe the clinical course of reflux regurgitation during the first year of life.

## SUBJECTS AND METHODS

A cohort study comprised of healthy newborns aged 1 month who attended the well-baby clinic of Songklanagarind Hospital in Southern Thailand was conducted. A newborn who had a history of birth asphyxia, prematurity, congenital anomalies and underlying disease was excluded. All eligible newborns were then followed every 2 months at regular well-baby clinic visits for one year.

Data collection from each infant at the beginning of the study and the follow-up period included :

- history of reflux symptoms including regurgitation, rumination, hematemesis, chronic cough, recurrent cyanosis or apnea, recurrent pneumonia or pulmonary wheezing, nocturnal irritability, and Sandifer-Sutcliffe syndrome,
- the standard deviation scores (Z) of body weight and length for age (in reference to NCHS standard),
- type of milk fed and amount of solid food intake.

Since regurgitation is the most obvious clinical manifestation of infantile GER, data regarding the frequency of symptoms in terms of day of symptoms in a week and the number of reflux episodes per day were collected. To date, there has been no a uniform clinical criteria to diagnose GER based on the number and frequency of regurgitation episodes. GER in this study was therefore operationally defined as regurgitation which occurred in an infant at least one day per week. The severity of reflux was classified, in a similar fashion to Carr's study<sup>6</sup>, into 3 categories according to the number of days of symptoms per wk, namely; 1-3 days per week, 4-6 days per week, and daily regurgitation.

For the parent or caretakers of a GER infant, a diary was provided for recording the occurrence of regurgitation in their infant. Using this diary, objective information about the

frequency of regurgitation in the infant was obtained. During the follow-up period, the GER infants were considered to be free of symptoms when their regurgitations did not occur as shown in the diary for at least 4 consecutive weeks. Investigations such as barium swallowing studies or esophageal pH studies were considered only in infants suspected of having pathologic GER on clinical grounds or having symptoms possibly related to occult GER.

Infants with uncomplicated reflux regurgitation were conservatively treated by reassuring the parents about the physiological nature of the symptoms and advice to avoid predisposing factors to regurgitation such as suddenly changing the position of the infant or abdominal compression after feeding.

*Statistical analysis* : The sample size of 100 healthy newborns was calculated statistically, based on the prevalence of GER in early infancy of 50% from a previous study ( $p = 0.5$ )<sup>7</sup> with 95% confidence and 10% precision. However, 200 newborns were included in this study to allow for a 50% dropout rate. Data were analysed using version 6 of Epi Info statistical package (CDC, Atlanta/WHO, Geneva). The influence of type of milk fed on the prevalence of reflux regurgitation was evaluated by using univariate comparison between infants with and without GER. Differences were considered statistically significant if  $P < 0.05$ .

This study was approved by the ethics committee of the Faculty of Medicine, Prince of Songkla University. All parents were fully informed of the nature of study and verbally informed consent was required from them before recruitment.

## RESULTS

Between March-June 1998, 216 healthy newborns entered this prospective survey. However, 71 infants were withdrawn from the study : 4 were excluded because their parental diaries were missing; 64 had incomplected one-year follow-ups and 3 developed serious diseases during the follow-up period. The remaining 145 infants were eligible for further analysis. These were 81 (55.9%) male and 64 (44.1%) female infants.

*Prevalence and clinical course of GER.* No pathologic GER or other GER symptoms apart from regurgitation were observed in this study. Of 145 infants who completed the one-year follow-up, we found that the prevalence of reflux regurgitation peaked at 2 months and decreased significantly at 4, 6, and 8 months (Table 1). At 12 months of age, only 7.6% of infants had reflux regurgitation. At each follow-up during this cohort study, it was observed that approximately 90% of Thai infants with GER had infrequent regurgitation of only 1-3 episodes per day (Table 1). Correspondingly with a decrease in the prevalence, the severity of regurgitation decreased dramatically with increasing age. As shown in the figure, the percentage of infants who regurgitated daily decreased from 42% at 1 month to only 5.2% at 6 months of age. From 6 to 12 months of age, almost all infants regurgitated only 1-3 days per week.

The effect of reflux regurgitation on the body weight of the infants was not demonstrated in this study as there was no significant difference in the mean standard deviation scores of body weight for age of infants with and without GER during the one-year of follow-up (Table 2).

*Type of milk fed and prevalence of GER.* The influence of the type of milk fed on the prevalence of GER was evaluated in infants of under 2 months of age which is the period of exclusive milk feeding. Dietary history revealed that the percentages of infants who



received breast milk, cow's milk formula, and breast milk combined with cow's milk were 27.6%, 10.3% and 62.1% at 1 month and 26.2%, 20.7% and 53.1% at 2 months, respectively. Weaning to solid foods was introduced in 90.2% of 4-months-old infants and all infants by 6 months of age. When infants aged 1 to 2 months were categorized into 3 groups according to the type of milk fed, the prevalences of reflux regurgitation among the 3 groups of infants were not significantly different (Table 3).

## DISCUSSION

To our knowledge, the natural course of reflux regurgitation in infants has apparently been reported only from Western countries<sup>6-8</sup>. The study described herein is the first known report concerning epidemiology of GER in Asian infants. When comparing the results of this study with those of Western studies, some interesting points are observed.

Carr', in a study of the natural course of GER associated with a hiatal hernia in English infants, showed that 60-65% of the infants were symptom-free by 2 years of age, 30% had persisting regurgitation into childhood, and 5% developed an esophageal stricture<sup>6</sup>. Shepherd et al. demonstrated that active management of infantile GER resulted in a more favorable clinical course<sup>8</sup>. According to their study, 81% of infants were symptom-free by 18 months of age, with 55% improvement by 10 months, and only 2% had persisting symptoms beyond 2 years of age. The results from these Western studies are obviously in contrast to our study as it found that half of our GER infants were symptom-free by 6 months and only 7.6% still had regurgitation on follow-up at one year of age. Such discrepancy in the natural course of infantile GER between Thai infants and Western infants may be, in part, accounted for by the difference in character of the study population. Whereas our subjects were selected from healthy infants at a well-baby clinic, the subjects in both Western studies were referred or hospitalized infants in whom the more severe symptoms of GER were always encountered.

Therefore it might be more reasonable to compare our results with the more recent and similar type of population-based study of Nelson et al., which was a cross-sectional survey for the prevalence of GER by using standardized questionnaires among 948 parents of American infants aged 13 months and younger<sup>7</sup>. They defined GER as regurgitation of at least 1 episode daily. In spite of a difference in diagnostic criteria, when applying Nelson's definition to our infants, we found that the prevalence of GER in Thai infants was 42.1%,

22.2%, 11.5%, 5.6% and 0% at 1 month, 2 months, 4 months, 6 months and 8-12 months, respectively. These prevalences in Thai infants are very much lower than American infants, reported as 50% at 0-3 months, 67% at 4-6 months, 21% at 7-9 months and 5% at 10-12 months. Moreover, it appears that American infants with GER had more episodes of regurgitation per day. Between the age of 1 and 6 months, regurgitation of 4 episodes per day or more was constantly reported by 20% of American infants, compared with 14% at 1 months of age in Thai infants and declining to only 3% at 6 months. Almost all Thai infants with GER regurgitated only 1-3 episodes per day.

Our findings that the symptoms of GER in Thai infants improved spontaneously with increasing age are in agreement with the results of previous Western studies. However it is noteworthy in Thai infants that the significant improvement of GER symptoms was evident at a very early age of 4 months and the improvement was markedly obvious between 4 and 6 months. The explanation for this observation is probably related to the weaning practice in Thailand, where introduction of solid foods is generally recommended at 4 months of age. Previous studies suggested that the increased viscosity of thickened feedings resulted in a decrease in clinical reflux regurgitation<sup>9,10</sup>, and this measure is still recommended for management of uncomplicated infantile GER<sup>11</sup>. In our series, introduction of solid foodings was initiated in 90% of infants at 4 months with an average amount of  $106.6 \pm 83$  ml. per day.

An interesting question to date is whether GER is more prevalent in formula-fed infants than in breast-fed infants. This question is raised because Heacock et al., in a study examining 24 hrs esophageal pH in 74 healthy infants, showed that breast-fed infants had lower esophageal pH reflux indices than the formula-fed infants<sup>12</sup>. Furthermore, a slower gastric emptying time was demonstrated in bottle-fed infants<sup>13</sup>, as a consequence, transient relaxation of the lower esophageal sphincter induced by an increase in intragastric pressure is

more susceptible. Recently, it has been suggested that GER in infants can be a secondary response to cow's milk protein allergy<sup>14</sup>. This evidence would indicate that bottle-fed infants are more likely to develop GER. However, the effect of type of milk on the prevalence of GER was not demonstrated in our study. This may be due to an insufficient size of study population. To verify such an effect, perhaps a further population-based study with a large sample size is needed.

Our study indicates that the racial differences in the nature of GER, as has been observed previously in adults, is also evident in infants. One may raise a question of whether the prevalence of gastroesophageal reflux disease (GERD) in Thai infants differs from that in Western infants, which has been estimated at 5-8%<sup>15</sup>. Although our study does not directly give the answer to this question, it may be anticipated that the prevalence of GERD is possibly much lower in Thai infants, when considering that reflux regurgitation in almost all Thai infants was resolved by one year of age and pathologic or complicated GER was not seen at all in our series. In our experience between 1997-1999 in Songklanagarind Hospital, which is a large tertiary hospital, GERD accounted for only 4% of consultations in our pediatric gastroenterology clinic, and most of these cases were neurological handicap patients. Given these facts, it would seem that disorders relating to GER are primarily a condition of the West. Interestingly, there is no word in the Thai language describing reflux symptom like "heartburn" in English. This may reflect the rarity of GERD in Thais.

Genetic or environmental factors or both are certainly responsible for the racial difference in the nature of GER. We believe that a difference in genetic background is more likely to play a major role since recent evidence indicates that both pediatric and adult onset GER have major genetic components<sup>16,17</sup>. Furthermore a gene on chromosome 13 q 14 for severe pediatric GER has been recently demonstrated<sup>18</sup>. Whether the variation in GER-related

genomes plays a major role in the differences in epidemiology among different ethnicities is therefore an interesting subject and needs to be clarified by further cross cultural genetic studies.

In summary, our study contributes more data about the epidemiology of infantile GER, particularly in non-Western countries, that will be beneficial for understanding the nature of GER of children in general. We found that the nature of reflux regurgitation in Thai infants differs from that of Western infants. In this regard, a practical implication for management of GER in Thai infants is noted. Instead of using Carr's data, we recommend our results as a reference for Thai pediatricians in providing advice and reassurance to Thai parents about the clinical course of reflux regurgitation. For Thai infants who still have frequent regurgitations beyond 6 months of age, non-physiologic GER should be given special attention.

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**Table 1.** *Prevalence of GER and frequency of regurgitation in Thai infants*

	Age (months)						
	1	2	4	6	8	10	12
No of GER infants	115	126	101	66	33	18	11
Prevalence	79.3	86.9	69.7	45.5	22.8	12.4	7.6
(95% CI)	(72.6-86)	(81.4-92.4)	(62.3-77.1)	(37.5-53.5)	(16.1-29.5)	(7.1-17.7)	(3.3-11.9)
Frequency of regurgitation*							
(No. of episodes/day)							
1-3	85.7	93.2	93.8	96.6	100	100	100
4-6	9.8	5.1	4.2	3.4	0	0	0
> 6	4.5	1.7	2.0	0	0	0	0
Mean no. of regurgitation/day	2.3	1.9	1.8	1.4	1.2	1.0	1.3
(SD; range)	(1.8; 1-10)	(1.2; 1-8)	(1.2; 1-7)	(0.8; 1-5)	(0.4; 1-3)	(0.2; 1-2)	(0.5; 1-2)

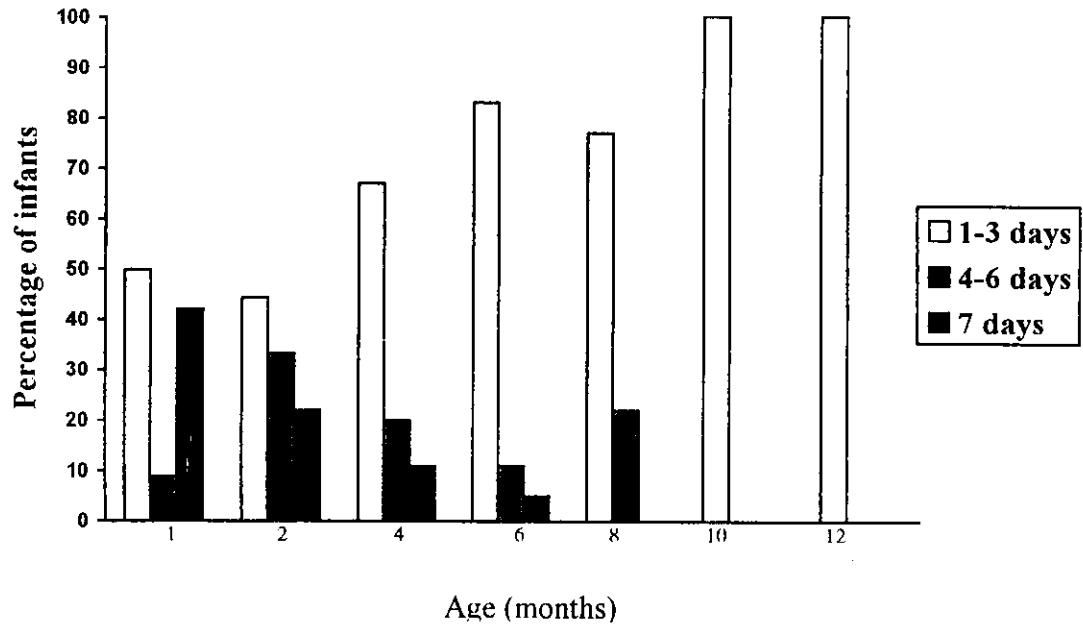
\* Expressed as a percentage of infants in each age group

**Table 2.** *Comparison of mean (SD) standard deviation scores of body weight for age of infants with and without GER*

Age (mo)	GER	No GER	P values (Student's t-test)
1	0.154 ± 0.897	0.197 ± 0.801	0.812
2	0.389 ± 0.837	0.292 ± 0.697	0.631
4	0.199 ± 0.817	0.217 ± 0.905	0.910
6	-0.062 ± 0.791	-0.026 ± 0.950	0.810
8	-0.363 ± 0.853	-0.412 ± 0.928	0.786
10	-0.502 ± 0.924	-0.513 ± 0.847	0.958
12	-0.655 ± 0.995	-0.624 ± 0.916	0.917

**Table 3** *Type of milk fed and the prevalence of reflux regurgitation*

Age (months)	1		2	
GER	no	yes	no	yes
Type of feeding (no., %)				
breast-fed	7 (17.5)	33 (82.5)	5 (13.2)	33 (86.8)
bottle-fed	5 (33.3)	10 (66.7)	3 (10)	27 (90)
combined	18 (20)	72 (80)	11 (14.3)	66 (85.7)
P value ( $X^2$ , Pearson)	0.419		0.840	



**Figure** Changing of severity of GER (days of symptoms per week) with age.