

Natural Evolution of Regurgitation in Children Aged 12-24 Months: A 1-year Cohort Study

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ABSTRACT

Background: There are very limited cohort studies regarding long term outcome of gastroesophageal reflux diseases (GERD), especially until 24 months old. The aim of this study is to see the natural history of GERD in 12-24 months old children based on their clinical signs and symptoms.

Method: Prospective one year population base cohort study involving 262 children. Their regurgitation history and GERD symptoms were recorded every two months.

Results: Two hundred and fifty three children completed the study. Seventy three children (27.8%) were still having regurgitation when they were 6 months old, 44 (16.7%) until 9 months old, and 24 (9.2%) until 12 months old. During 12 months follow-up the prevalence and frequency of regurgitation decreased to 2.4% and 1.2% in the age of 18 and 24 months respectively. Infant with regurgitation at 6 months old were 13.2 times more likely to have regurgitation at 12 months old (RR = 13.2; 95% CI = 4.8-36.6). Prevalence of regurgitation after 18 months old were 37 times higher risk compared to those not regurgitating at the age of 12 months (RR = 37; 95% CI = 2.2-613.9). GERD symptoms were higher in children that were still regurgitating until 9 months old 64.5% (RR = 2.3; 95% CI = 1.7-3.0) compared to those only experiencing until 6 months old 54.7% (RR = 1.3; 95% CI = 1.7-3.0).

Conclusion: Regurgitation decrease during 12-24 months old period. The history of regurgitation in 6 and 9 months old is related to the probability to become GERD in 12-24 months old period.

Keywords: gastroesophageal reflux, children 12-24 months, GERD symptoms

ABSTRAK

Latar Belakang: Penelitian kohort jangka panjang dari penyakit refluks gastroesophageal (PRGE) terutama sampai usia 24 bulan masih sangat terbatas. Tujuan penelitian ini adalah untuk melihat perjalanan alamiah dari PRGE pada usia 12-24 bulan berdasarkan gejala klinis.

Metode: Penelitian kohort prospektif selama satu tahun di populasi yang melibatkan 262 pasien anak di Jakarta. Riwayat regurgitasi dan gejala PRGE yang timbul dilakukan pencatatan setiap dua bulan.

Hasil: Dua ratus lima puluh tiga pasien anak menyelesaikan penelitian ini. Tujuh puluh tiga (27,8%) masih mengalami regurgitasi saat usia 6 bulan, 44 (16,7%) sampai usia 9 bulan, dan 24 (9,2%) sampai usia 12 bulan. Selama 12 bulan pemantauan, prevalensi dan frekuensi regurgitasi menurun menjadi 2,4% dan 1,2% pada usia 18 dan 24 bulan. Bayi dengan riwayat regurgitasi pada usia 6 bulan mempunyai risiko 13,2 kali lebih besar untuk mengalami regurgitasi pada usia 12 bulan dibanding mereka yang tidak mempunyai riwayat regurgitasi pada usia 6 bulan (RR = 13,2; 95% CI = 4,8-36,6). Anak yang masih mengalami regurgitasi pada usia 12 bulan mempunyai risiko 37 kali lebih besar untuk mengalami regurgitasi pada usia 18 bulan (RR = 37; 95% CI = 2,2-613,9). Gejala GERD lebih tinggi pada anak-anak yang masih regurgitasi sampai berusia 9 bulan, 64,5% (RR = 2,3; 95% CI = 1,7-3,0) dibanding dengan mereka yang hanya mengalami sampai usia 6 bulan, 54,7% (RR 1,3; 95% CI = 1,7-3,0).

Simpulan: Prevalensi regurgitasi menurun selama periode usia 12-24 bulan. Riwayat regurgitasi pada usia 6 dan 9 bulan berkaitan dengan kemungkinan menjadi PRGE pada anak dengan usia 12-24 bulan.

Kata kunci: refluks gastroesofagus, anak usia 12-24 bulan, gejala klinis penyakit refluks gastro esofagus

INTRODUCTION

Regurgitation (spilling, spitting) as major symptom of gastro-esophageal reflux (GER) is a common phenomenon in children which occurs very frequently during infancy. Natural history of GER is very important. This allows doctors to manage infants with GER to provide evidence-based advice to parents. Studies from Europe, US, and Asia showed that 60-80% of healthy infants aged 0-1 months had at least one episode of regurgitation each day. Regurgitation episodes decreased according to age, reaching 40-60% in 4-6 months of age, and 4-5% after the age of 12 months.¹⁻³

GER may occur with additional symptoms and complications that are known as GER diseases (GERD). Few study showed that feeding problems in children may have been related to excessive regurgitation (GER) during their infancy.⁴⁻⁶ Children with GERD had a higher incidence of feeding problems. Otherwise, most of the studies are cross-sectional, or retrospective.⁷⁻¹² No population based cohort study on the natural history of GER had been performed towards the 12-24 months old period. This paper explains a population based study exploring the natural history of GERD in 12-24 months old children based on their clinical signs and symptoms. We also tried to associate them with their history of regurgitation during infancy.

METHOD

This 1 year prospective cohort study screened all children in one district area of south Jakarta, Indonesia. Out of 403 children aged 12 months who managed to be approached to join this study, 262 children were eligible to be enrolled. In order to be eligible for inclusion, infants had to be born full-term, good nutritional status or at least mild malnutrition (body weight to length \geq 70% according to CDC-2000 growth chart) at the time of enrollement, no chronic/severe condition that need long term follow-up include delayed development, did not received any treatment for vomiting, and medication such as appetite modulator, cisapride, H₂ antagonist, or proton pump inhibitor in the last two months. Education level of mother was at least senior

high school and worked as housewives, also able to be contacted by telephone if needed. The exclusion criteria were non-permanent residence of Jakarta (or high probability to move to another town in the next 1 year), had congenital abnormalities, and parents refused to sign informed consent.

At the time of the enrollment, all children were examined for baseline anthropometric data (body weight (BW) and body length (BL)). All parents were informed about GER especially the natural history and complications. The data were obtained by interviewing the parents using a standard questionnaire about the history of regurgitation during 0-12 months of age, and GERD symptoms. After the baseline data obtained, and every 2 months parents were asked to bring their children to the study base camp to be examined by investigator.

Body weight was measured using calibrated digital weighing scale. Body length were also measured by trained staff. Parents were asked for the history of regurgitation and GERD symptoms of their children during the last two weeks prior to each visit. Children were also examined for ongoing illness. Data of regurgitation frequency during two weeks (14 days) were then divided by 14 and considered as daily regurgitation frequency. Two weeks were chosen since parents can still memorize things happening to their children well enough. We did not choose to use parents' notes since having them write notes everyday was technically difficult.

GERD symptoms were defined as: (1) feeding problem, (2) nocturnal awakening, (3) back arching, (4) gastrointestinal bleeding, (5) abdominal pain, or (6) body weight did not gain in two months period. Feeding problems itself were defined as child refused to eat or to open their mouth to eat although they were seen hungry; or food kept in the mouth for a long time (did not want to swallow food); or almost always vomited the food that had been swallowed; or took a long time to finish the meal (duration were also asked); or mothers feel bad to see their children feeding habit.

In statistical analysis, Chi-square test was used for 2 x 2 tables. For paired data, we used McNemar test. Normal distributed data were analyzed using T-independent test,

while abnormal distributed data were analyzed using non-parametric (Mann-Whitney) test. If $p < 0.05$, was considered statistically significant.

RESULTS

Two hundred and sixty-two infants age 12 months were enrolled in this study. During 12 months follow-up, 9 children (3.4%) were dropped-out from the study because move to another town (3 parents) or refused to continue the study (6 parents). Among 253 subjects who completed the study, 133 (52.6%) were male and 120 (47.4%) were female.

Out of 262 children enrolled in this study, 73 (27.8%) were still having regurgitation when they were 6 months old, 44 (16.7%) until 9 months old, and another 24 (9.2%) until 12 months old. Among the 24 children regurgitating until the age of 12 months, 20 were having regurgitation symptoms since 6 months old, while another 4 since 9 months old (Figure 1). Among the 262 children enrolled in this study, 73 (27.8%) had been breastfed exclusively until 6 months old, while from the 24 with regurgitation until 12 months old, only 9 of them received the 6 months exclusive breastfeeding.

During the 12 months follow-up the prevalence and frequency of regurgitation decreased. Among the 24 (9.2%) still regurgitating until 12 months old, the

prevalence decreased to 2.4% and 1.2% in the age of 18 and 24 months respectively. Likewise among the 15 out of 24 (62.5%) children age 12 months with frequency of regurgitation 1-4 times a day, decreased to only 1 out of 5 (20%) during the 18 months period, and after 24 months there were no children regurgitating 1-4 times per day. The other 9 out of 24 (37.5%) regurgitating < 1 times a day during age 12 months old, progressed to 3 out of 3 regurgitating at the age of 24 months. During the follow up period there were no children reported to have > 4 times regurgitation a day (Table 1).

Regurgitation at Aged 12, 18 and 24 Months

Vomiting or regurgitation after the age of 12 months is associated with history of regurgitation during their infancy period. Prevalence of regurgitation in children aged 12 months is much higher in those having regurgitation until 6 months old compared to those not having regurgitation (27.4% vs. 2.1%; $p < 0.001$). Infant with regurgitation at 6 months old were 13.2 times more likely to still having regurgitation at 12 months old (Table 2). Prevalence of regurgitation after 18 months old in those still having regurgitation at the age of 12 months is 25%, with a 37 times higher risk compared to those not regurgitating at the age of 12 months (Table 3).

Three of 6 of children regurgitating at the age of 18 months still have those symptoms until 24 months old, although these were not statistically significant. In other words, children with regurgitation at the age of 18 months old did not have increased risk of still having regurgitation until 24 months old (Table 4).

GERD Symptoms

During the 12 month follow up, number of children with GERD symptoms are different in relation to the history of regurgitation during their infancy, which are 27.8% infants still regurgitating until 6 months old, and 16.8% infants at the age of 9 months. GERD symptoms is higher in children that were still regurgitating until 9 months old 64.5% (RR = 2.3; 95% CI = 1.7-3.0)

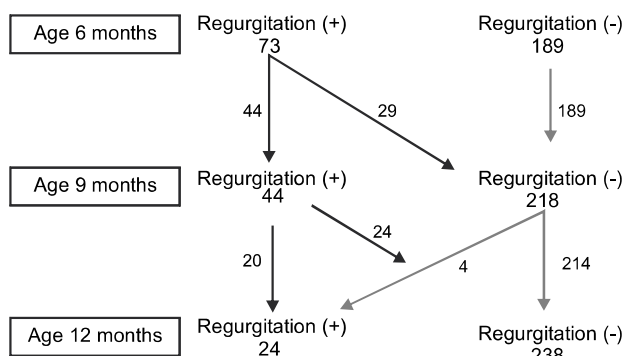


Figure 1. Children following this study and their regurgitation profile

Table 1. Prevalence of regurgitation in children age 12-24 months

Age (month)	Number children	Number children with regurgitation				Total
		No regurgitation	Regurgitation (time /day)			
			< 1	1-4	> 4	
12	262	238	9	15	0	24 (9.2%)
14	262	245	14	3	0	17 (6.5%)
16	258	244	12	2	0	14 (5.4%)
18	254	248	5	1	0	6 (2.4%)
20	253	248	5	0	0	5 (1.9%)
22	253	249	4	0	0	4 (1.6%)
24	253	250	3	0	0	3 (1.2%)

compared to those only experiencing until 6 months old 54.7% (RR = 1.3; 95% CI = 1.7-3.0) (Table 5).

GERD symptoms shown by the infants include feeding refusal (31.29%), do not want to swallow the food (16.56%), vomiting after feeding (14.11%), need long time to feed (30.10%). Body weight did not gain in 2 months period 0.61%.

Anthropometrics Data at 12, 18 and 24 Months

Children with persistent regurgitation showed a significantly less mean body weight at 12 months (8.32 (SD = 1.06) vs. 8.90 (SD = 1.08); p < 0.001), 18 month (9.45 (SD = 1.24) vs. 10.29 (SD = 1.41); p < 0.001), and 24 months age (10.76 (SD = 1.68) vs. 11.38 (SD = 1.57); p = 0.004) (Table 6).

Likewise the percentage of ideal body weight to body length also showed no significant difference between three groups at 12 months of age, while a significant less percentage BW/BL was found at 18 and 24 months. The mean percentage BW to BL at 18 months was 88.67 (SD = 7.27), p = 0.009 and median percentage BW to BL at 24 months was 90.4 kg (range 84.3–96.9), p = 0.002 respectively (Table 7).

DISCUSSION

Gastroesophageal reflux is a common problem in infants. Regurgitation is one of the most prominent clinical manifestations that were found in infants. Thus, the prevalence of regurgitation is often associated

Table 2. Association of regurgitation at age 12 months and history of regurgitation at age 6 months (n = 262)

History of regurgitation at aged 6 months	Number children with regurgitation at aged 12 months		RR (95% CI)
	Regurgitation (+)	Regurgitation (-)	
Regurgitation (+)	20	53	13.2 (4.8-36.6)
Regurgitation (-)	4	185	

Statistical analysis with McNemar test, p < 0.001

Table 3. Association regurgitation at age 18 months and history of regurgitation at age 12 months (n = 254)

History of regurgitation at aged 12 months	Number children with regurgitation at aged 18 months		RR (95% CI)
	Regurgitation (+)	Regurgitation (-)	
Regurgitation (+)	6	18	37 (2.2-613.9)
Regurgitation (-)	0	230	

Statistical analysis with Mc Nemar test, p < 0.001

Table 4. Association regurgitation at age 24 months and history of regurgitation at age 18 months (n = 253)

History of regurgitation at aged 18 months	Number children with regurgitation at aged 24 months		RR (95% CI)
	Regurgitation (+)	Regurgitation (-)	
Regurgitation (+)	3	3	7 (0.36-135.5)
Regurgitation (-)	0	247	

Statistical analysis with McNemar Test, p 0.13

Table 5. GERD symptoms in children 12-24 months related with history of regurgitation during infancy

History of regurgitation at	Number children	GERD symptoms at age 12-24 months		p	RR (95% CI)
		Yes	No		
6 months	Yes	73	40	0.04	1.3 (1.0-1.8)
	No	189	76		
9 months	Yes	44	31	< 0.001	2.3 (1.7-3.0)
	No	218	67		

Statistical analysis with Chi-square test; GERD: gastro-esophageal reflux disease

Table 6. Body weight regarding to regurgitation at 12, 18, and 24 months old

Age (months)	Body weight regarding to regurgitation (mean (SD))		p
	Yes	No	
12	8.32 (1.06)	8.90 (1.08)	< 0.001
18	9.45 (1.24)	10.29 (1.41)	< 0.001
24	10.76 (1.68)	11.38 (1.57)	0.004

Statistical analysis with T independent test

Table 7. Body weight/body length regarding to regurgitation

Age (months)	BW/BL regarding to regurgitation		p
	Yes	No	
12 (mean (SD))*	89.67 (8.4)	92.38 (9.7)	0.215
18 (mean (SD))*	88.67 (7.27)	92.37 (9.5)	0.009
24 (median (range))#	90.4 (84.3-96.9)	93.3 (88.3-99.2)	0.002

*Statistical analysis with T independent test; #Statistical analysis with Mann-Whitney test; BW: body weight; BL: body length

with prevalence of GER. Prevalence of GER usually decreases concomitantly with the increase of age.^{2,11,13} However, some study reported that feeding difficulties in children may have been related to excessive regurgitation during their infancy.^{7,8,10,14} There are many studies about prevalence and natural history of GER in infants from western and eastern country. But, very limited study report about long term outcome, natural history and evolution of GER, especially until 24 months old of age. Most of the studies are cross sectional or retrospective and no population based cohort study had been performed until 24 months old period.¹⁰⁻¹²

During 1 year cohort of our study we found that prevalence of regurgitation at age of 12, 18, and 24 months old is respectively decreased from 9.2%, 2.4% to 1.2%. Of 262 infants participated in the study, 73 (27.9%) had regurgitation at 6 months of age and 20 (7.6%) at the age of 12 months. This data is much lower than the data reported by previous studies.^{9,10,12,16,17} Osatakul reported prevalence of regurgitation at 6 months of aged about 45.5%, whereas Campanozzi reported about 72%, De 41% and Nelson reported 61%. At 12 months old, previous study by Osatakul reported prevalence of regurgitation is about 7.6%, whereas Campanozzi found 39% of infants still having regurgitation. Miyazawa found no infants have regurgitation at 12 months old. Data from India concluded 14.8% infants were still having regurgitation for about 14.8% during 6-12 months old period and 10.2% during 12-24 months period. Data from Indonesia found that 18.8% infants still having regurgitation at 6-12 months period.² By the age of 24 months old, Nelson reported that prevalence of regurgitation decreased to 2%.¹¹ This wide range variation of data might be caused by variation of method used for GER diagnosis. But from all of the report, we can summarize that there is the same pattern of GER evolution that is decreasing prevalence from 6 to 24 months old period. Frequency of regurgitation decreased during period 12-24 months old. No infants were having regurgitation for more than 4 times a day since 12 months old. The highest proportion is infants

at 1-4 time regurgitation groups. Osatakul and Hegar reported no infant has regurgitation for > 4 times a day at 12 months old.^{2,16} Whereas Nelson still found about 2% infants having regurgitation at age 12 months.¹⁰ Decreasing prevalence and frequency of GER might be cause by maturation of LES, gravitation since infants starting to sit and walk, and also introduction of solid food.¹¹

In our study, we try to find the association between history of the last 6 months regurgitation and the occurrence of further regurgitation. Risk of having regurgitation still increased until 18 months old according to history of the last 6 months experience of regurgitation. At 24 months old, risk of regurgitation was not influenced more by history of regurgitation at the last 6 months. There is limited study support this finding. But, we predict that this finding were associated with the natural evolution of GER in which that the symptoms decrease until the age of 18 months than has no consistent pattern afterwards. Campanozzi also conclude that the natural history of GER will resolve at age 18 months old.¹⁷

This study also finds history of regurgitation at 6 months and 9 months old increased risk of infants for having GER disease at age of 12-24 months old. Infants that regurgitate more than 90 days during their first 2 years of life were at higher risk (RR = 2.3) of developing GER diseases.¹⁴ Nelson conclude that infant that regurgitated during age 6-12 months had difficulty to eat 4.2 times more than those without history of regurgitation.¹⁰ Feeding refusal as one of the symptoms of GERD was found in 32% children of our study. This data is also higher than the previous reports which taken by recall methods. Limited study has been performed to see the association between duration of GER and the probability for becoming GER disease.

Studies by Campanozzi et al, Miyazawa et al, and Osakatul et al showed that there were no differences in weight gain between those with or without regurgitation.^{12,16,17} Although other study by De et al showed that children with GERD have inadequate weight gain compared to those without GERD.⁹ Our

study compared BW of infants at age 12, 18, 24 months who were having regurgitation and not. This study find that infants who were still having regurgitation at 12, 18, and 24 months have lower BW compared to whom were not regurgitating. This finding may be associated with higher number of GERD symptoms that occurs in this study. Other factors must be considered whether regurgitation is associated with weight gain, such as low social and economy status, low educational status, neglect by parents, feeding difficulties, impaired interaction between children and their parents, and depression experienced by the parents.

CONCLUSION

This study found that symptoms of regurgitation decrease during 12-24 months old period. However, after 18 months old, we cannot find the consistent pattern of regurgitation evolution. The history of regurgitation in age 6 and 9 months old is related to probability for becoming GERD in 12-24 months old period. Therefore, GERD symptoms should be explore in children with history of regurgitation more than 6 months old and prompt management should be done to prevent GERD complications in later life.

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