Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.65, No.3 (2025). p.224-31; DOI: https://doi.org/10.14238/pi65.3.2025.224-31

Original Article

Gastroesophageal reflux in premature infants and the incidence of apnea, desaturation, and bradycardia events

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Abstract

Background The diagnosis of gastroesophageal reflux in premature infants is often based on clinical symptoms, namely apnea, desaturation, and bradycardia. This may lead to overdiagnosis and overtreatment in the management of gastroesophageal reflux.

Objective To determine the relationship between gastroesophageal reflux with apnea, desaturation, and bradycardia in premature infants.

Methods This cross-sectional study was done in premature infants with post-menstrual age of 32-36 weeks who had a history of apnea, desaturation, or bradycardia and suspected of having reflux. The subjects had no history of using prokinetic drugs or gastric acid suppressants, were not using advanced respiratory support, and had no congenital abnormalities. Gastroesophageal reflux was assessed using multiple intraluminal impedance – pHmetry for 24 hours.

Results From a total of 20 subjects, there were 3,882 reflux events over 24 hours. Of these, 331 reflux events (8.5%) reached the upper esophageal sphincter. Two subjects (10%) had a reflux index ≥10%, indicating a risk of developing reflux esophagitis. Reflux contents were mostly liquid (79.9%) and weak acid (84.6%). The proportion of high reflux accompanied by apnea and bradycardia was very small (0.3%). High reflux was not associated with desaturation.

Conclusion In our study, reflux occured in all premature infants, but only 10% of them had risk of reflux esophagitis. There were no associations between reflux and apnea, desaturation, or bradycardia. Therefore, these symptoms should not be used as the basis to diagnose reflux, much less to justify prescribing proton pump inhibitor drugs. **[Paediatr Indones. 2025;65:224-31; DOI: https://doi.org/10.14238/pi65.3.2025.224-31**].

Keywords: *gastroesophageal reflux; apnea; desaturation; bradycardia; preterm infants*

Gastroesophageal reflux (GER) is defined as the backflow of stomach contents into the esophagus, which may or may not be accompanied by regurgitation. Stomach contents that remain in the esophagus for too long and too frequently can lead to esophagitis or gastroesophageal reflux disease (GERD). Premature infants are the most vulnerable age group to experience GER due to functional immaturity of the lower esophageal sphincter (LES).[1] The current hypothesis is that reflux can stimulate laryngeal constriction and vagal nerve activation. Therefore, diagnosis of GER in premature infants is often based solely on clinical symptoms, especially episodes of apnea, desaturation, and bradycardia.[2,3] Subsequently, those clinical symptoms are used as a basis for giving medication, especially proton pump inhibitors (PPIs).[2] Malcolm *et al.*[4] studied 1,598 very low birth weight infants and found that 47.6% of discharged

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Submitted October 29, 2024. Accepted June 3, 2025.

infants received anti-reflux therapy. In other words, overdiagnosis and overtreatment may occur in the management of reflux in premature infants in everyday practice. On the other hand, PPIs have been reported to cause various complications in infants, such as upper and lower respiratory tract infections, diarrhea, and constipation.[5]

The existing data show that the occurrence of apnea, desaturation, and bradycardia in premature infants is mostly due to central nervous system abnormalities (63%).[6] However, to date, many doctors, including in Indonesia, still prescribe PPIs as initial therapy for premature infants with these symptoms, including in Indonesia. Identifying the characteristics of GER in premature infants, especially in Asian countries, is still needed to strengthen existing findings and provide doctors with greater confidence in administering rational management.

Methods

This observational, analytic study using a cross-sectional design was done in 2023 in the Perinatology Ward of Dr. Cipto Mangunkusumo Hospital (CMH), a tertiary hospital in Indonesia. Inclusion criteria were 1) premature infants with a gestational age of 32-36 weeks, 2) infants with a history of apnea, desaturation, or bradycardia at least once within 24 hours suspected to be due to reflux, 3) already received nutrition from breast milk/formula with a minimum volume of 60 mL/kg/day for 24 hours, and 4) parental consent to participate in the study. Exclusion criteria were 1) infants still requiring advanced respiratory support [intubated or using non-invasive positive pressure ventilation (NIPPV)], 2) history of using drugs with prokinetic or gastric acid suppression effects, 3) presence of major intracranial or congenital abnormalities, or 4) infants with sepsis .

The MII-pH device (*Ohmega®*) was used in this study. The examination procedure began with calibrating the device in pH 4.0 and pH 7.0 buffer solutions. The electrode was then positioned until the pH sensor was 1 cm above the lower esophageal sphincter (LES) (**Figure 1**). The test commenced after 30 minutes of probe attachment to avoid hypersalivation effects, followed by data collection for 24 hours, including frequency, duration, acidity, type, and height of the reflux. Hemodynamic monitoring was conducted for 24 hours. Subjects were positioned

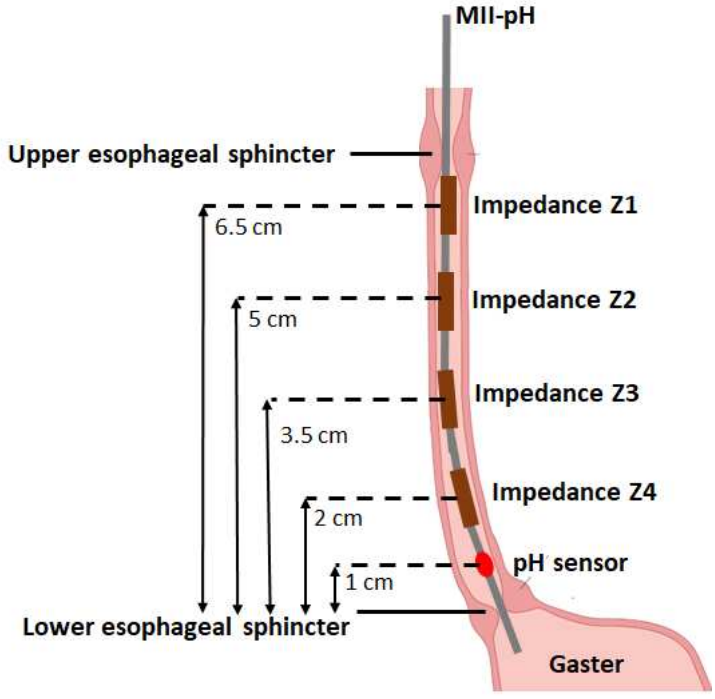

Figure 1. The position of MII-pH in the esophagus

supine at a 45° angle with the head elevated, following standard care procedures. Therefore, the infant's position during feeding was not considered as a variable under investigation.

Several reflux classifications were used in this study. Based on the acidity level, reflux was divided into acid reflux (pH<4), weakly acidic (pH 4-7), and non-acidic (pH>7). Impedance in the device was useful for evaluating height, type, and bolus clearance time of the reflux. Reflux height above the LES was divided into 2 cm (impedance Z4), 3.5 cm (impedance Z3), 5 cm (impedance Z2), and 6.5 cm (impedance Z1). Impedance Z1 was located just below the upper esophageal sphincter (UES). Reflux that reached the impedance Z1 was referred as high reflux (**Figure 1**). Reflux index was defined as the percentage of total time when the pH of the lower esophagus was <4. Reflux index was divided into physiological reflux (reflux index <5%) and pathological reflux (reflux index ≥5%). Pathological reflux may irritate the lining of esophagus. It is believed that individuals with a reflux index ≥10% are likely to have reflux esophagitis.[7] Type of reflux was divided into liquid and liquid-gas combination. Apnea was defined as a cessation of breathing for 20 seconds or more, or if less than 20 seconds accompanied by bradycardia, desaturation, cyanosis, or pallor.[8] Desaturation was defined as a decrease in oxygen saturation <88% for ≥10 seconds.[9] Bradycardia was defined as a heart rate <100 beats per minute.[8] Apnea, desaturation, or bradycardia events were considered reflux-related if they occured within 3 minutes after the reflux event.[10] This study was approved by Ethics Committee of the Faculty of Medicine, Universitas Indonesia.

Results

A total of 20 subjects met the inclusion criteria of the study. During the monitoring of MII-pH, no clinical worsening or other conditions requiring increased oxygen supplementation were observed. Therefore, all subjects successfully followed the study protocols until the end.

The number of male and female subjects was equal. Almost all subjects were born via caesarean section. The mean gestational age of subjects was 31.5 weeks, ranging from 28 to 35 weeks. The mean birth weight of subjects was 1,377 grams, with 80% of subjects having a birth weight appropriate for gestational age. At the time of data collection, the mean age of subjects was already within 34 weeks of postmenstrual age (PMA), with a mean weight of 1,812 grams and a body length of 41.6 cm (**Table 1**). Forty percent of subjects received only breast milk. Most subjects received milk every 3 hours (70%), with slow drip administration. All subjects received full feed nutrition with an average milk volume of 148.3 mL/kg/day via orogastric tube (OGT). The most commonly used oxygen supplementation was continuous positive airway pressure (45%); 35% of subjects no longer required oxygen supplementation for at least 24 hours.

Table 1. Subjects' characteristics

Characteristics	(N=20)
Gender, n	
Male	10
Female	10
Birth characteristics	
Delivery methods, n	
Vaginal	1
Caesarian section	19
Mean gestational age weeks (SD)	31.5 (2.4)
Median birth weight (range), grams	1,377 (750-2,830)
Birth weight category, n	
Appropriate for gestational age	16
Small for gestational age	4
Mean post menstrual age (SD), weeks	34.1 (1.3)
Mean body weight (SD), gram	1,812 (507)
Mean body length (SD), cm	41.6 (2.9)
Type of milk, n	
Breast milk	8
Formula milk	5
Combination	7
Frequency of milk feeding, n	
Every 2 hours	6
Every 3 hours	14
Milk administration, n	
Gravitational	2
1-hour drip	11
2-hour drip	7
Mean volume per milk feeding (SD), mL	28.9 (2.9)
Mean volume of milk per day (SD), mL/kg	148.3 (32.6)
Oxygen supplementation, n	
Without	7
Low flow	4
Continuous positive airway pressure	9

Of the 20 subjects, there were 3,882 reflux events detected, with 3,407 (87.8%) events detected only up to the level of the pH sensor, and the rest reaching the impedance sensor (**Figure 2**). Out of the 475 reflux events detected by the impedance sensor, 69.7% were classified as high reflux. The mean reflux frequency across all subjects was 194 refluxes per day (**Table 2**); approximately one-fifth were acid refluxes. Of all the acid refluxes, the lowest average pH was 2.2. Three subjects had pathological reflux, consisting of 1 (5%) subject with a reflux index of 5-10, and 2 (10%) subjects highly likely to have experienced reflux esophagitis (reflux index ≥10). Of 475 reflux events reaching the impedance sensors, the majority of reflux contents were of the liquid type (79.9%) and weakly acidic (84.6%). Among all high reflux events, the median bolus clearance time was 2.8 seconds (**Table 3**).

Subjects receiving low-flow oxygen therapy had higher reflux frequency and reflux index, but the differences were not significantly different compared to subjects with CPAP or room air. Type of milk given, feeding frequency, and feeding duration were also not significantly associated with reflux frequency or reflux index (**Table 4**).

The proportion of reflux accompanied by symptoms of apnea and bradycardia was very small, with only one out of 331 high reflux events (0.3%),

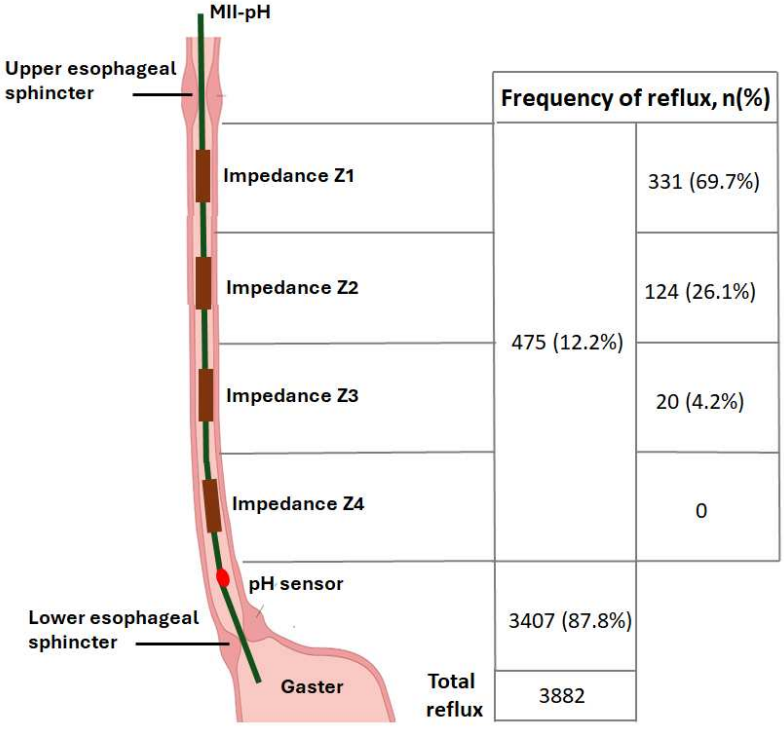

Figure 2. The frequency of reflux

Table 2. Characteristics of reflux events detected by pH sensor

Description	(N=20)
Mean reflux frequency within 24 hours per subject (SD)	194.1 (103.5)
Median acid reflux frequency within 24 hours per subject (range)	41 (0-214)
Mean lowest pH (SD)	2.2 (0.9)
Reflux index, n	
<5	17
5-10	1
≥10	2

rendering the potential relationship statistically not significant. Reflux was also not associated with the occurrence of desaturation within 3 minutes (**Table 5**). Furthermore, no significant differences were found in the number of episodes of apnea, desaturation, and bradycardia between subjects in the physiological and pathological reflux groups (**Table 6**).

Table 3. Characteristics of reflux reaching the impedance sensor

Variables	(N=475)
Median reflux frequency within 24 hours per subject (range)	13 (0-93)
Type of reflux, n(%)	
Liquid	373 (79.9)
Combination of liquid and gas	102 (20.1)
Reflux acidity, n(%)	
Acidic (pH<4.0)	72 (15.2)
Weakly acidic (4 ≤ pH<7)	402 (84.6)
Non-acidic (pH ≥ 7)	1 (0.2)
Median bolus clearance time of high reflux (range), seconds	2.8 (1.2-17.9)

Table 4. Analysis of oxygen supplementation and feeding strategies on reflux

Variables	Mean reflux frequency (SD)	P value	Mean reflux index (SD)	P value
Oxygen supplementation				
Without	180.7 (71.4)	0.756	1.6 (0.6)	0.403
Low flow	229.8 (151.6)		5.2 (3.7)	
CPAP	188.7 (110.4)		3 (1.2)	
Type of milk given				
Breastmilk	225.7 (41.4)	0.534	1.7 (0.4)	0.518
Formula	184.4 (40.9)		3.2 (1.9)	
Combination of breastmilk and formula	164.9 (37.7)		4.2 (2.2)	
Feeding frequency				
Every 2 hours	137.1 (30.4)	0.1	1.6 (0.5)	0.32
Every 3 hours	218.5 (28.5)		3.6 (1.3)	
Feeding duration				
Gravitational	194.5 (119.5)	0.45	0.5 (0.3)	0.31
Pump 1 hour	168.6 (24.5)		2.3 (0.7)	
Pump 2 hours	234 (46.4)		4.8 (2.3)	

Table 5. Analysis of high reflux and desaturation (N=475 events)

Reflux, n(%)	Desaturation within 3 minutes after reflux		OR (95%CI)	P value
	Positive (n=28)	Negative (n=447)		
High	20 (6.1)	311 (93.9)	1.09 (0.47 to 2.54)	0.84
Non-high	8 (5.6)	136 (94.4)		

Table 6. Analysis of the frequency of apnea, desaturation, and bradycardia in the physiological and pathological reflux groups

Within 3 minutes after reflux	Physiological reflux (n=17)	Pathological reflux (n=3)	P value
Median apnea (range)	0 (0-1)	0	0.69
Median desaturation (range)	0 (0-18)	0 (0-2)	0.88
Median bradycardia (range)	0 (0-1)	0	0.69

Discussion

This research explored the relationships between gastroesophageal reflux and the occurrence of apnea, desaturation, and bradycardia in premature infants capable of full feeding. Subjects had a mean gestational age of 31.5 weeks and mean birth weight of 1,377 grams. Four subjects (20%) had birth weights classified as small for gestational age. The reflux index measurements in these four subjects did not correspond to a predilection for reflux esophagitis. This finding differed from the retrospective study by Forssell et al., who collected data from patient registries from 1973 to 2007 and diagnosed esophagitis based on endoscopic examination. Their results indicated that being small for gestational age at birth was one of the risk factors for esophagitis (OR 1.58; $P<0.05$).[11]

A similar study in premature infantsshowed that the median reflux detected by pH sensors within 24 hours was 71 reflux episodes. The mean reflux within 24 hours was 2.7 times higher in our study, amounting to 194 reflux episodes.[12] This difference may have occurred because the pH sensor probe in another study was placed higher, at 2 cm above the LES. To date, there have been no global guidelines regarding the positioning of pH sensors above the LES, but placing them 2 cm above the LES is generally indicated for older children (over 1 year of age) who ingest larger meal or drink volumes.[13]

Using impedance sensors, the type of esophageal bolus, reflux height, and bolus clearance can be observed. Reflux height is crucial to assess because high reflux may reach the UES and potentially cause clinical symptoms such as apnea, desaturation, or bradycardia. In our study, among all reflux events detected by impedance sensors, 15.2% were acid reflux, 84.6% were weakly acidic reflux, and 0.2% were non-acid reflux. These results are similar to a previous study which found that among all reflux events detected in premature infants, 25.4% were acid reflux, 72.9% were weakly acidic reflux, and none were non-acid reflux.[12] Thus, weakly acidic reflux was the most common type of reflux. Almost all studies have found that PPIs are not beneficial in treating weakly acidic reflux, either in reducing symptoms or preventing aspiration.[14,15] To establish that a patient has esophagitis due to reflux and requires PPI therapy, pH monitoring must be performed as the gold standard. In our study, only two subjects (10%) were found to have a risk of reflux esophagitis. However, these subjects did not exhibit typical alarm symptoms, such as irritability after feeding, hematemesis, melena, or back-arching.

In our study, the majority of reflux events (69.7%) detected by impedance sensors reached the proximal esophagus. Similar results were obtained in a study which found that approximately 85.7% of reflux reached the proximal esophageal segment during the post-prandial phase.[12] Another study found that the mean reflux height detected by impedance sensors was 5.5 cm, with the highest reaching 7.4 cm.[16] Our study found that the median bolus clearance time in the proximal esophagus was 2.8 seconds. Our result was similar to the findings of a study which reported 3.8 seconds.[17] In other words, esophageal motility was not a problem in the majority of subjects in our study.

Gastric distension due to aerophagia is believed to increase the risk of reflux.[18] We found that reflux frequency and reflux index were not related to the oxygen supplementation used by the subjects. One study assessing gastroesophageal reflux (GER) in patients with obstructive sleep apnea (OSA) found that CPAP puts pressure on the esophagus, which indirectly increases the muscle tone of the lower and upper esophageal sphincters, helping to prevent reflux.[19]

In our study, the type of milk given was not associated with the reflux frequency or reflux index. However, Chen et al. found that near-term (>35 weeks) and full-term infants who received formula milk had a 1.95-fold higher risk of reflux compared to those who received breast milk.[20] This difference may have been due to factors such as sample size or research methods. Chen et al. recruited 2,841 infants and data were collected via telephone interviews with mothers. Feeding milk every two or three hours was not associated with the reflux frequency or reflux index in our study. Similar studies are still limited, but a meta-analysis suggested that feeding milk every two or three hours did not impact the outcomes such as time to reach full feed or feeding intolerance.[21]

We did not find differences in reflux frequency or reflux index between patients receiving milk by rapid gravity or slow drip. Slow drip feeding reduced reflux frequency, but did not affect the reflux index.[22]

Factors that need further investigation to explain these differences include the volume of milk given and the age of subjects. We used a similar volume of milk to that used in a previous study.[22] However, in their study, there was a statistically significant age difference between the rapid gravity group (PMA 42 weeks) and the slow drip group (PMA 45 weeks). This age difference likely affected the maturity of the lower esophageal sphincter.

We found that the proportion of reflux events followed by apnea and bradycardia within 3 minutes after reflux was very small, at 0.3%. In this study, we also found no significant difference in the incidence of desaturation between high reflux and non-high reflux. Similar results were obtained from two other studies on premature infants.[23,24] This reinforces that although, hypothetically, high reflux is believed to cause cardiorespiratory events through stimulation of the larynx and vagal nerve, research findings from various studies to date have not been able to prove this hypothesis. We also found that the reflux index (physiological or pathological) was not associated with the frequency of apnea, desaturation, or bradycardia events.

Overdiagnosis of GER and overtreatment with PPI administration occur in both developed and developing countries. A survey in America found that 40-50% of neonatologists believed apnea was caused by GER and 20-40% argued that pharmacological therapy was necessary.[25] From collected data on the types of anti-reflux medications commonly used for premature infants in various countries, of all the infants receiving anti-reflux therapy, 61% in America received H_2 receptor antagonists, 56% in Australia received PPIs, 72% in Thailand received domperidone, and 78% in Lebanon received domperidone. These data indicate that global guidelines for managing GER are not entirely aligned.[26] The results of our study are expected to serve as a basis for not diagnosing GERD solely based on clinical symptoms of apnea, desaturation, or bradycardia. Furthermore, the use of PPIs as reflux therapy is expected to become more rational.

Several limitations of our study should be noted: 1) the number of subjects was too small to identify alarm symptoms of desaturation caused by high reflux, and 2) we did not evaluate microaspiration as the link between reflux and the occurrence of apnea, desaturation, or bradycardia.

All premature babies experience reflux, but only 10% are at risk of reflux esophagitis. There is no correlation between reflux and the occurrence of apnea, desaturation, or bradycardia in premature babies. Apnea, desaturation, and bradycardia in premature babies cannot be used as clinical indicators of pathological reflux or as a basis for administering PPIs.

Conflict of interest

None declared.

Funding acknowledgment

The authors received no specific grants from any funding agency in the public, commercial, or not-for-profit sectors.

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