

# Prevalence of gastroesophageal reflux disease found by pH measurements in preterm infants with suggestive symptoms

Carlos Alberto Velasco Benítez,<sup>1\*</sup> Ernesto León Vallejo Mondragón,<sup>2</sup> Mauricio Alberto Arévalo Sanabria.<sup>3</sup>

<sup>1</sup> Pediatrician, Gastroenterologist, Nutritionist, and Senior Professor at Universidad del Valle in Cali, Colombia

<sup>2</sup> Pediatrician, Cardiologist and Professor at Universidad Libre, Seccional Cali in Cali Colombia

<sup>3</sup> Pediatrician, Neonatologist, and Assistant Professor at Universidad del Valle in Cali, Colombia

\*Correspondence: [carlos.velasco@correounivalle.edu.co](mailto:carlos.velasco@correounivalle.edu.co).

Received: 12/10/18

Accepted: 04/02/19

## Abstract

**Introduction:** Gastroesophageal reflux is a common physiological phenomenon in preterm infants and is frequently diagnosed in neonates for whom it is an important clinical phenomenon. **Objective:** To determine the prevalence and symptoms of gastroesophageal reflux disease (GERD) by 24-hour ambulatory esophageal pH monitoring of preterm neonates. **Methodology:** This is a study of the prevalence of GERD among patients in the Neonatal Intensive Care Unit of Cali, Colombia. Esophageal pH of infants was monitored when GERD was suspected. In addition, sociodemographic and clinical variables were recorded and taken into account. Univariate analysis by means of measures of central tendency and bivariate analysis were performed using the chi-squared test and Student's T test with  $p < 0.05$  established as significant. **Results:** Twenty preterm newborns whose ages from birth ranged from 27.6 days to 36.5 days and whose gestational ages ranged from 3.8 weeks to 31.6 weeks were included. Twelve were male, and eleven (55.0%) had abnormal pH. Gastric waste and heart disease were associated with abnormal pH. **Conclusion:** The prevalence of GERD found through pH monitoring was relatively high in this group of infants compared findings in the world literature although no clear associations were found between the symptoms analyzed and other factors except for heart disease and gastric waste.

## Keywords

Newborn, prevalence, gastroesophageal reflux, esophageal monitoring.

## INTRODUCTION

Gastroesophageal reflux (GER) is defined as the return of the gastric contents to the esophagus, with or without regurgitation or vomiting. It must be distinguished from gastroesophageal reflux disease (GERD) which includes a series of GER symptoms. These can affect a child's quality of life and cause pathological complications such as failure to grow, problems with eating and/or sleeping, chronic respiratory problems, esophagitis, hematemesis, apnea and life-threatening events. (1, 2) GER is a common physiological phenomenon in preterm infants which is frequently diagnosed in neonatal intensive care units (NICU). It can lead to prolonged hospital stays and high in-hospital

costs which makes it an important clinical phenomenon in NICUs. (3, 4)

GER in preterm infants is often diagnosed and managed based on clinical manifestations rather than specific paraclinical tests. In addition, there is little evidence of the damage caused by GER in preterm infants, so questionable anti-GER drugs are routinely used in this age group. (4)

Nonspecific signs and symptoms attributable to GER include food intolerance or aversion, poor weight gain, frequent regurgitation, apnea, oxygen desaturation, bradycardia, arching and irritability. (1, 3, 4)

Classically, pH monitoring (pHm) in the lower esophagus has been used to diagnose GER in children and adults. Two methods are in use: 24-hour outpatient esophageal pH

monitoring and multichannel intraluminal impedance testing (MII). MII measures esophageal movements of liquids, solids and air by electrical impedance, and it shows whether movements are antegrade or retrograde while it simultaneously measures pH. (5) The normal reference values for pH monitoring in preterm infants are those of Ng et al. (6)

The objective of this study is to determine the prevalence and symptoms of GERD by pHm in preterm infants at the Hospital Universitario del Valle (HUV) Evaristo García in Cali, Colombia.

## MATERIAL AND METHODS

This observational, descriptive, non-experimental, cross-sectional and comparative study was conducted in preterm infants who were hospitalized in the Newborn Intensive Care Unit of the Hospital Universitario del Valle (HUV) Evaristo García in Cali, Colombia between January and June 2013. Infants diagnosed as premature who had pathologies typical of GER such as respiratory distress syndrome, sepsis and metabolic disorders were included.

Premature newborns with symptoms suggestive of GERD such as desaturation during feeding, bloating, vomiting, unexplained apnea, residue, coughing, crying, irritability, life-threatening events and lack of weight gain not attributable to another pathology were included. Preterm infants who had already received anti-reflux medications were excluded. Before starting the study, members of the families of the preterm infants were told the nature and purpose of the investigation and had opportunities to request more information and discuss any questions they may have had. All infants were being fed enterally at the time of the study. Some of those with nasogastric feeding in situ were also in their normal sleeping position, whether supine or prone.

Each preterm infant underwent outpatient esophageal pH monitoring for a minimum of 20 continuous hours. Monitoring was preceded by a 4-hour fast. A disposable 1-channel pediatric catheter with antimony tip was attached to a Mark III pH monitor from Synetics Medical that had been calibrated before the study with buffer solutions at pHs of 4.0 and 7.0. The length of catheter to be introduced through one of the infant's nostrils was calculated on the basis of the formula of Strobel et al. ( $\text{size} \times 0.252 + 5 \times 0.86$ ). (7) It was corroborated by a portable chest x-ray which helped locate the tip of the catheter between the sixth and eighth thoracic vertebrae. Once in place, the catheter and monitor were secured with surgical tape to prevent displacement for duration of pHm. Symptoms and signs present during the procedure were registered.

Synetics Medical software was used to analyze pH plots which were then interpreted according to the standard normal values developed by Ng et al. The reflux index,

the number of acid episodes, the number of acid episodes longer than 5 minutes and the duration of the longest acid episode were all included in the analysis. (6)

The statistical analysis performed with the Stata 15 software included measures of central tendency such as percentages, averages and standard deviations and univariate analysis using the chi-square test ( $\chi^2$ ) and Student's t test with  $p < 0.05$  considered to be significant.

The risk of this study was classified as minimal according to Resolution 8430 of 1993 of the Ministry of Health of Colombia which established ethical standards of research with human beings. The rights and welfare of each participant were guaranteed in accordance with the Helsinki Declaration. Before a patient was included in the study, parents or guardians signed an informed consent document allowing data to be used in research and ensuring confidentiality and professional handling of the study's data and results.

## RESULTS

### General Characteristics

An observational, descriptive, non-experimental, cross-sectional, comparative study of 20 preterm infants was performed. Average post-birth age was  $36.5 \pm 27.6$  days, average gestational age was  $31.6 \pm 3.8$  weeks, average weight was  $1493.3 \pm 579.8$  grams, and the average Ballard Maturational Assessment Score was  $31.6 \pm 3.7$  weeks. Twelve of the infants were male, 18 were mixed race, and 17 were from Cali, Colombia. The mothers' average age was  $25.0 \pm 7.4$  years old. Ten had had no prenatal monitoring, ten infants were born as part of multiple births two of which were vaginal and eight of which were caesarian. Infants were hospitalized because they were premature and had pathologies such as respiratory distress syndrome, sepsis and metabolic disorders.

### Outpatient Esophageal pH Monitoring

Eleven of the 20 preterm infants (55.0%) had abnormal esophageal pH measurements (Table 1).

**Table 1.** Measurements of esophageal pH for eleven outpatient preterm infants at the Hospital Universitario del Valle (HUV) Evaristo García in Cali, Colombia

Variable	Average (n = 11)	Normal values according to Ng et al. (6)
Study duration (hours)	21.4	
Reflux Index (%)	18.1	$0.7 \pm 1.1$
Number of acid episodes	157	$7.6 \pm 11.2$
Number of acid episodes > 5 minutes	13.7	$0.5 \pm 1.1$
Longest episode (minutes)	70	$4.6 \pm 6.1$

## Signs and Symptoms Found in Outpatient Esophageal pH Monitoring

Residues and heart disease in these infants was associated with abnormal pH-measurements (Table 2).

**Table 2.** Signs and symptoms and outpatient esophageal pH measurements in 20 preterm infants at the Hospital Universitario del Valle (HUV) Evaristo García in Cali, Colombia

pH measurement			p	pH measurement			p
Normal	Abnormal			Normal	Abnormal		
Cyanosis			0.203	Cough			0.085
Yes	5	4		Yes	6	5	
No	15	7		No	14	6	
Apnea			0.086	Respiratory distress syndrome			0.996
Yes	11	8		Yes	11	6	
No	9	3		No	9	5	
Vomiting			0.303	Regurgitation			0.731
Yes	13	6		Yes	8	4	
No	7	5		No	12	7	
Gastric residuals			0.024	Abdominal distension			0.85
Yes	10	3		Yes	3	1	
No	10	8		No	17	10	
Drooling			0.281	Necrotizing enterocolitis			0.38
Yes	1	0		Yes	1	1	
No	19	11		No	19	10	
Failure to gain weight			1	Irritability			0.38
Yes	1	1		Yes	1	1	
No	19	10		No	19	10	
Cardiopathy			0.001	Sepsis			0.673
Yes	3	3		Yes	10	5	
No	17	8		No	10	6	
Use of aminophylline			0.605	Use of antibiotics			0.196
Yes	8	5		Yes	18	9	
No	12	6		No	2	2	

## DISCUSSION

The use of pH-measurement including multichannel intraluminal impedance is relatively common for investigation of gastroesophageal reflux disease (GERD) in preterm infants (preterm infants). It is performed on between 24.0% (8) and 32.0% of the patients in neonatal care units. (9) Some authors believe that the validity of GERD diagnostic tests, including pH monitoring, cannot be estimated on the basis of current knowledge. They argue for clinical trials to determine the usefulness of these and other tests. (10-12).

According to the current Practical Clinical Guidelines for Pediatric Gastroesophageal Reflux of the North American Society of Pediatric Gastroenterology, Hepatology and

Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN), when pHm cannot be done with MII, other pHm methods should be used to correlate persistent symptoms with acid gastroesophageal reflux events. (2) This study uses pHm, which detects more episodes of reflux than does MII according to Rossor et al. (13)

## Prevalence of GERD in Preterm Infants

More than half of the preterm infants studied in the Newborn Intensive Care Unit of the HUV of Cali, Colombia had abnormal pH. These data are very similar to those described by Di Fiore et al. (14) who reported that 59.0% of their study participants had GERD diagnosed by pHm. The percentage diagnosed with GERD in our study was greater than the percentages identified Sivalingam et al., Rossor et al. and of Funderburk et al. who found of 30.0%, 21.0%, and 10.0% respectively using MII. (13, 15 16)

Prevalence variability could be the result of different techniques and different interpretations of results used to diagnose GERD. Other factors that could account for these variations include sociodemographic characteristics and differences in postnatal and/or gestational ages from one study to another. This implies a need for greater standardization in subsequent analyses. Similarly, results may be influenced by the total number of preterm infants studied. A small sample is likely to have a higher prevalence since the population analyzed is suspected of having GERD.

## Signs and Symptoms Associated with GERD in Preterm Infants

Few studies mention associations between symptoms and GERD which is why indices have been used to interpret MII/pHm for diagnosis of GERD in neonates. Nevertheless, a study by Barriga Rivera et al. of neonates with cardio-respiratory symptoms has failed to demonstrate that the symptom index (IS), the symptom sensitivity index (ISS) and the probability of association of symptoms (PAS) are useful for this purpose. (17) The relationship between GERD and cardiorespiratory events in neonates is controversial. (18) In our results, children with heart disease without respiratory symptoms had abnormal pH more often than did children without heart disease ( $p < 0.05$ ). These data are similar to those found by Qureshi et al. (19). They found that 6.1% of cardiorespiratory symptoms during sleep were associated with events diagnosed as GERD using MII/pHm and concurrent polysomnography.

In this study, there were no preterm infants with apparently life-threatening events, but Macchini et al. reported them in 80.0% of the children diagnosed with GERD by

pHm. (20) Although GERD and apnea occur frequently in preterm infants as shown by Rossor et al., (21) we found no association between GERD and apnea. Gastric residue was found in a statistically significant percentage of the infants with abnormal pH in our study, but more observation of the feeding of these infants is required to identify other possible confounders. Although we did not take into account whether preterm infants were stimulated by non-nutritive sucking, a cross-sectional study of preterm infants by Corvaglia et al. has suggested that it is reasonable to use pacifiers with these neonates since their use had no effects on acid and non-acid GER evaluated by MII. (22)

Causality between reflux events and abnormal signs in preterm infants is limited. Given clinical suspicion of GERD in preterm infants, diagnostic procedures such as MII/pHm should be performed. (23) Nevertheless, Salvatore et al. have found poor correlation between parental reports of GERD symptoms, pHm results, and endoscopic evidence of GERD. (24) According to a study by De Rose et al., (25) MII/pHm not only plays a diagnostic role for preterm infants, it also offers prognostic value in terms of duration of drug treatment. In this therapeutic sense, Loots et al. (26) managed to demonstrate that administration of proton pump inhibitors, either omeprazole at 1 mg/kg/day or esomeprazole at 0.5 mg/kg/day for 2 weeks, improves the integrity of the esophageal mucosa in infants between 0 and 6 months of age who have been diagnosed with GERD by MII/pHm.

Weaknesses of this study include those associated with the type of feeding and with gastric residue of preterm infants fed by nasogastric tube in terms of quantification, volume, children with or without nasogastric tube, whether gastric residues were present or absent, and whether the infants were prone or supine. The use of a nasogastric tube can be a confusing factor as well as a risk factor for increased episodes of GERD while episodes of GERD in prone position are minor.

In conclusion, the prevalence of GERD diagnosed by pH monitoring in preterm infants in this study was relatively high compared to results found in the world's literature. No clear associations with the symptoms analyzed, except for heart disease and gastric waste, were found. Finally, we were unable to analyze these associations due to lack of knowledge in terms of quantification, volume, and presence or absence of nasogastric tubes and positions. This emphasizes the need for further studies to determine possible associations and appropriate management of GERD.

## REFERENCES

1. Czinn SJ, Blanchard S. Gastroesophageal reflux disease in neonates and infants: When and how to treat. *Pediatr Drugs*. 2013;15:19-27. doi: 10.1007/s40272-012-0004-2.

2. Rosen R, Vandenplas Y, Singendonk M, Cabana M, Di Lorenzo C, Gottrand F, et al. Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr*. 2018;66(3):516-554. doi: 10.1097/MPG.0000000000001889.
3. Kültürsay N. Gastroesophageal reflux (GER) in preterms: Current dilemmas and unresolved problems in diagnosis and treatment. *Turk J Pediatr*. 2012;54:561-9.
4. Eichenwald EC. Diagnosis and Management of Gastroesophageal Reflux in Preterm Infants. *Pediatrics*. 2018;142(1). pii: e20181061. doi: 10.1542/peds.2018-1061.
5. Velasco Benítez CA. GERD in children: An update | Actualización sobre enfermedad por reflujo gastroesofágico en niños. *Rev Colomb Gastroenterol*. 2014;29:55-62.
6. Ng SCY, Quak SH. Gastroesophageal reflux in preterm infants: Norms for extended distal esophageal pH monitoring. *J Pediatr Gastroenterol Nutr*. 1998;27:411-4. doi: 10.1097/00005176-199810000-00009.
7. Strobel CT, Byrne WJ, Ament ME, Euler AR. Correlation of esophageal lengths in children with height: Application to the Tuttle test without prior esophageal manometry. *J Pediatr*. 1979;94:81-4. doi: 10.1016/S0022-3476(79)80361-3.
8. Rossor T, Andradi G, Bhat R, Greenough A. Investigation and management of gastro-oesophageal reflux in United Kingdom neonatal intensive care units. *Acta Paediatr*. 2018;107:48-51. doi: 10.1111/apa.14073.
9. Dhillon AS, Ewer AK. Diagnosis and management of gastro-oesophageal reflux in preterm infants in neonatal intensive care units. *Acta Paediatr Int J Paediatr*. 2004;93:88-93. doi: 10.1080/08035250310007934.
10. Díaz JJ. ¿Podemos diagnosticar adecuadamente el reflujo gastroesofágico en niños? *Evid Pediatr*. 2013;9:59.
11. Ochoa C, de Llano A. La validez de las pruebas diagnósticas de la enfermedad por reflujo gastroesofágico en la infancia es dudosa. *Evid Pediatr*. 2013;9:63.
12. van der Pol RJ, Smits MJ, Venmans L, Boluyt N, Benninga MA, Tabbers MM. Diagnostic accuracy of tests in pediatric gastroesophageal reflux disease. *J Pediatr*. 2013;162(5):983-7. e1-4. doi: 10.1016/j.jpeds.2012.10.041.
13. Rossor T, Lingam I, Douiri A, Bhat R, Greenough A. Detection of gastro-oesophageal reflux in the neonatal unit. *Acta Paediatr Int J Paediatr*. 2018;107:1535-40. doi: 10.1111/apa.14315.
14. Di Fiore J, Arko M, Churbock K, Hibbs A, Martin R. Technical limitations in detection of gastroesophageal reflux (GER) in neonates. *J Pediatr Gastroenterol Nutr*. 2009;49:177-82. doi: 10.1097/MPG.0b013e318195d7b3.
15. Sivalingam M, Sitaram S, Hasenstab K, Wei L, Woodley F, Jadcheria S. Effects of esophageal acidification on troublesome symptoms: an approach to characterize true acid GERD in dysphagic neonates. *Dysphagia*. 2017;32:509-19. doi: 10.1007/s00455-017-9792-4.



16. Funderburk A, Nawab U, Abraham S, DiPalma J, Epstein M, Aldridge H, et al. Temporal association between reflux-like behaviors and gastroesophageal reflux in preterm and term infants. *J Pediatr Gastroenterol Nutr.* 2016;62:556-61. doi: 10.1097/MPG.0000000000000968.
17. Barriga-Rivera A, Moya MJ, Lopez-Alonso M. El índice de síntomas binomial para la evaluación de la asociación temporal entre síntomas cardiorrespiratorios y reflujo gastroesofágico en neonatos. *An Pediatr.* 2016;85:232-9. doi: 10.1016/j.anpedi.2015.09.024.
18. Lopez-Alonso M, Moya MJ, Cabo JA, Ribas J, del Carmen Macias M, Silny J, et al. Twenty-Four-Hour Esophageal Impedance-pH Monitoring in Healthy Preterm Neonates: Rate and Characteristics of Acid, Weakly Acidic, and Weakly Alkaline Gastroesophageal Reflux. *Pediatrics.* 2006;118:e299-308. doi: 10.1542/peds.2005-3140.
19. Qureshi A, Malkar M, Splaingard M, Khuhro A, Jadcheria S. The role of sleep in the modulation of gastroesophageal reflux and symptoms in NICU neonates. *Pediatr Neurol.* 2015;53:226-32. doi: 10.1016/j.pediatrneurol.2015.05.012.
20. Macchini F, Morandi A, Cognizzoli P, Farris G, Gentilino V, Zanini A, et al. Acid Gastroesophageal Reflux Disease and Apparent Life-Threatening Events: Simultaneous pH-metry and Cardiorespiratory Monitoring. *Pediatr Neonatol.* 2017;58:43-7. doi: 10.1016/j.pedneo.2015.12.005.
21. Rossor T, Andradi G, Ali K, Bhat R, Greenough A. Gastro-Oesophageal Reflux and Apnoea: Is There a Temporal Relationship? *Neonatology.* 2018;113:206-11. doi: 10.1159/000485173.
22. Corvaglia L, Martini S, Corrado MF, Mariani E, Legnani E, Bosi I, et al. Does the Use of Pacifier Affect Gastro-Esophageal Reflux in Preterm Infants? *J Pediatr.* 2016;172:205-8. doi: 10.1016/j.jpeds.2016.01.022.
23. Corvaglia L, Mariani E, Aceti A, Capretti MG, Ancora G, Faldella G. Combined oesophageal impedance-pH monitoring in preterm newborn: Comparison of two options for layout analysis. *Neurogastroenterol Motil.* 2009;21:1027-32. doi: 10.1111/j.1365-2982.2009.01301.x.
24. Salvatore S, Hauser B, Vandemaele K, Novario R, Vandenplas Y. Gastroesophageal Reflux Disease in Infants: How Much is Predictable with Questionnaires, pH-metry, Endoscopy and Histology? *J Pediatr Gastroenterol Nutr.* 2005;40:210-5. doi: 10.1097/00005176-200502000-00024.
25. De Rose DU, Cresi F, Romano V, Barone G, Fundarò C, Filoni S, et al. Can MII-pH values predict the duration of treatment for GERD in preterm infants? *Early Hum Dev.* 2014;90:501-5. doi: 10.1016/j.earlhumdev.2014.07.003.
26. Loots CM, Wijnakker R, van Wijk MP, Davidson G, Benninga MA, Omari TI. Esophageal impedance baselines in infants before and after placebo and proton pump inhibitor therapy. *Neurogastroenterol Motil.* 2012;24(8):758-62, e351-2. doi: 10.1111/j.1365-2982.2012.01922.x.