CLINICAL PREDICTORS OF ABNORMAL ESOPHAGEAL pH MONITORING IN PRETERM INFANTS

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ABSTRACT - ***Background*** - Risk factors for gastroesophageal reflux disease in preterm neonates have not been yet clearly defined. ***Aim*** - To identify factors associated with increased esophageal acid exposition in preterm infants during the stay in the neonatal unit. ***Methods*** - A case-control study in preterm infants who had undergone prolonged monitoring of distal esophageal pH, following clinical indication. Eighty-seven preterms with reflux index (percentage of total time of esophageal pHmetry) ≥10% (cases) and 87 unpaired preterms were selected with reflux index <10% (controls). Demographic variables, signs and symptoms, main diagnoses and some aspects of treatment were studied. Simple and multiple logistic regression analysis adjusted for birthweight and postconceptional age at the pH study were used. ***Results*** - The factors associated with a greater chance of reflux index ≥10% in preterms were: vomiting, regurgitation, Apnea, female gender. The variables that were associated with a lower frequency of increased reflux index were: volume of enteral intake at the onset of symptoms ≥147 mL/kg/day, and postnatal corticoid use. ***Conclusions*** - Vomiting, regurgitation, apnea, female gender and acute respiratory distress during the first week of life were variables predictive of increased esophageal acid exposition in preterm infants with birthweight <2000 g. Bronchopulmonary dysplasia and use of caffeine were not associated with reflux index ≥10%.

HEADINGS - Gastroesophageal reflux. Gastric acidity determination. Risk factors. Infant, premature.

INTRODUCTION

In the past 10 years, a substantial increase has occurred in the number of studies on gastroesophageal reflux (GER) in preterm infants[11, 17, 26, 29]. However, many aspects concerning GER in the neonatal period remain controversial or have still to be clearly defined[21, 29, 31]. Despite the uncertainties, neonatal units worldwide continue to treat around 19% of preterm infants of less than 34 weeks of gestational age (GA) with empiric antireflux therapy[8, 36].

Retrograde flow of gastric contents to the esophagus is very common in healthy preterm[19], and may be characterized by vomiting or regurgitation without any other type of manifestation. The term gastroesophageal reflux disease (GERD) may be applied in complicated GER, if associated with low weight gain, anemia and irritability, or respiratory signs, such as apnea or laryngitis[35].

The wide use of antireflux therapy in newborn infants with clinical manifestation attributed to GERD has been discouraged[21, 31]. However, there is a physiological rationale that explains the relationship between GER and symptoms such as apnea[33], and evidence that clinical or surgical treatment may result in improvement or complete remission of symptoms[2, 13, 25].

Definitive diagnosis of GERD in preterms is difficult. In addition to the non-specificity of the signs and symptoms, laboratory investigation is hampered by a lack of gold standard tests for diagnosis in this age group[28]. Moreover, the previous reports, which are not conclusive about the relationship between symptoms and GER, they present some pitfalls because they have studied heterogeneous groups of infants with few digestive symptoms[29], inaccurate definition of GERD or short period with acid in esophagus[18]. The identification of the factors associated with abnormal esophageal pH monitoring in preterm infants with symptoms/signs attributed to GERD may help proper diagnoses and treatment of such disease.

The objective of this study was to identify the factors associated with increased acid esophageal exposition in preterm infants by using intra-esophageal pH assessment during hospitalization in a neonatal unit.

METHODS

An observational retrospective, case-control study was carried out. The study sample was selected from among all patients who had undergone prolonged distal intra-esophageal pH monitoring, following clinical

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indication by the medical team, between October 1995 and May 2002. Selection criteria comprised the following: birthweight <2000 grams and gestational age ≤37 weeks, as established by the date of last menstrual period or by using the method described by BALLARD et al.[3]. The cases included preterm infants with symptoms suggestive of GERD and reflux index (RI – percentage of the time that the esophagus is exposed to a pH of less than 4 during de recording period) ≥10%[34]. Likewise, the controls consisted of patients investigated for clinically suspected GERD and hospitalized during the same period of time as the cases; however, RI values of controls were <10%. The groups were unpaired and only one control was chosen for each case. Preterm infants were excluded from the study when their monitoring was performed under non-standardized conditions or when technical problems were encountered.

Esophageal pH was monitored using 1.5 mm catheters with an antimonium electrode (Synectics Medical, TX, USA) positioned in the distal third of the esophagus at the T6-T7 level. The position of the electrode was confirmed by chest x-ray. The Digitrapper MkIII (Synectics Medical, TX, USA) was used to record the data analyzed using the EsopHogram software program, version 5.60C4 (Gastrosoft Inc., TX, USA). The duration of monitoring ranged from 18 to 24 hours, and the infants remained in supine or prone position for equal time during the testing. The enteral intake was 130-140 mL/kg/day and feeding was given by bolus administration every 3 or 4 hours through a gastric tube. Caffeine, prokinetics and antacids were discontinued 48-72 hours prior to pH monitoring.

Clinical signs and symptoms, demographical characteristics, main clinical diagnoses and some therapeutic aspects of the infants were selected as independent variables. Signs and symptoms included >3 episodes/day of regurgitation or vomiting, always associated with other symptoms suggestive of GERD. Episodes of late onset apnea unresponsive to caffeine were considered as manifestations related to GERD[25]. Apneas that persisted beyond 36 weeks of postconceptional age[9] and acute life-threatening events requiring resuscitation or intermittent mandatory ventilation (IMV) comprised other indications. Isolated desaturations (<87%) or bradycardia (heart rate <80 bpm), back-arching and laryngeal stridor comprised other signs studied.

Other possible risk factors considered were: adequacy of weight for gestational age[4], acute respiratory distress (ARD) during the 1st week of life, bronchopulmonary dysplasia (BPD) [32], malformations of the central nervous system, perinatal asphyxia, periventricular leukomalacia and peri-intraventricular hemorrhage, grades III and IV. The procedures studied were the duration of use of gastric tube prior to pH monitoring, the volume of feedings at the onset of clinical manifestations, the use and duration of IMV and the continuous positive airway pressure (CPAP) in the 1st week of life.

Feeding intolerance was defined as dietary difficulties (abdominal distension, bilious or lactic residues of more than 50% of the previous feeding volume) that resulted in discontinuation of at least one feeding in the 1st days of the transition to enteral route. Pre- and postnatal corticoid, pulmonary surfactant, caffeine, opioids, dopamine and systemic bronchodilators were the drugs studied.

The SAS statistical software program, version 6.12 for Windows (SAS Institute Inc., NC, USA) was used for the statistical analysis. The chi-squared test was used to analyze the categorical variables between the two groups and the Mann-Whitney U test for the comparison of the numerical variables. Simple and multiple logistic regression analysis[14], adjusted for the variables of birthweight and postconceptional age (PCA) at the time of pH study, were used to establish the odds ratio (OR) and the 95% confidence intervals. The stepwise selection criteria was applied to the variables, taking into consideration those variables with $P<0.25$ in the univariate analysis. Significance was established as $P<0.05$. The institute's Internal Review Board approved the study protocol.

RESULTS

During the study period, 235 esophageal pH monitoring studies were carried out in 193 preterm infants. Studies of pH were routinely carried out whenever neonatal GERD was suspected except in patients in whom vomiting and regurgitation were the only symptom and in preterms with severe neurological impairments. Eighty-seven cases (RI ≥10%) and 87 controls (RI <10%) fulfilled inclusion criteria. The distribution of demographic data and the symptoms in the two groups are shown in Table 1.

There were no statistically significant differences between cases and controls with respect to the distribution of the symptoms except for vomiting and regurgitation, which were more common among cases (Table 1).

The moment of onset of symptoms was similar in both groups: 11.0 ± 7.9 days of life for cases and 12.8 ± 8.7 days for controls ($P = 0.165$). Evaluation of pH was carried out at an earlier PCA in cases than in controls (Table 1). Cases had a mean RI of 21.6% ± 9.6% (median = 18.9%; range = 10.3%-66.4%; 25P-75P = 14.5%-27.8%), whereas controls had a mean RI of 4.6% ± 2.9% (median = 4.5%, range = 0%-9.0%; 25P-75P = 2.5%-6.8%). Digestive malformations (n = 2), malformations of the central nervous system (n = 2), and necrotizing enterocolitis (n = 8) were infrequent and were not associated with any specific group. There were no cases of genetic syndromes.

The duration of use of gastric tube was more frequent in the control group: 47.7 ± 19.3 days (median 45, range 3-114) versus 42.5 ± 16.7 days (median 39, range 18-92) but this difference was not statistically significant ($P = 0.063$). In 119 newborn infants (68%), there was an association between symptoms and the volume of enteral intake, 58 of these infants being cases and 61 controls. The volume of the feeding immediately preceding the onset of symptoms was significantly lower in the cases compared to the controls: 73.5 ± 54.8 mL/kg/day (median 64.0) versus 95.7 ± 58.4 mL/kg/day (median 100.0) ($P = 0.036$).

Univariate logistic regression, adjusted for the variables birthweight and PCA, showed that RI ≥10% was significantly more frequent in female infants and in infants with vomiting and regurgitation (Table 2). Postnatal use of corticoids and a

TABLE 1. Distribution of the demographic variables and symptoms in cases (RI≥10%) and controls (RI<10%)

Variable	Cases (n = 87)	Controls (n = 87)	*P*-value
Birth weight (g) median (range)	1185 ± 290 1180 (650-1990)	1050 ± 310 985 (510-1950)	0.001*
Gestational age (wk) median (range)	28.9 ± 2.2 29.0 (24-35)	29.0 ± 2.5 29.0 (23-35)	0.839*
5-minute Apgar	8.0 ± 1.9	8.0 ± 2.0	0.789*
Female (n)	44	32	0.067†
SGA (n)	34	44	0.127†
Regurgitation (n)	26	8	<0.001†
Vomiting (n)	43	20	<0.001†
PCA at time of pH study (wk) median (range)	35.0 ± 2.5 34.7 (29-43)	35.8 ± 2.9 35.4 (30-42)	0.045*
Apnea (n)	82	76	0.115†
ARD (n)	72	65	0.195†
Bronchopulmonary dysplasia (n)	33	44	0.093†
PVH (n)	7	9	0.600†
Perinatal asphyxia (n)	8	6	0.577†
Periventricular leukomalacia (n)	6	6	1.000†
Feeding intolerance (n)	62	52	0.111†
IMV (n)	63	74	0.042†
Ventilation (d)	12.1 ± 12.4	17.7 ± 16.5	0.110*
CPAP (n)	61	70	0.114†
Surfactant (n)	23	17	0.280†
Caffeine (n)	70	71	0.847†
Bronchodilator (n)	23	39	0.011†
Dopamine (n)	37	45	0.224†
Opioid (n)	27	22	0.399†
Prenatal steroid (n)	49	43	0.362†
Postnatal steroid (n)	7	25	<0.001†

Values presented as mean ± SD; * Mann-Whitney U-test; † Chi-square test
g = gram; wk = week; d = day; n = cases; SGA = small for gestational age;
ARD= acute respiratory distress in the first week of life; IMV = intermittent mandatory ventilation; CPAP = continuous positive airway pressure; PCA = postconceptional age at the pH study; PVH = periventricular and ventricular hemorrhage grade III, IV

TABLE 2. Univariate logistic regression analysis (n = 174), adjusted for the birthweight and postconceptional age at time of pH study

Variable	*P*-value	OR	95% CI
For each week less of GA	0.125	0.84	0.68-1.05
Female	0.040	1.94	1.03-3.65
SGA	0.767	0.91	0.47-1.75
Regurgitation	0.001	4.58	1.85-11.33
Vomiting	<0.001	3.25	1.65-6.40
Bronchopulmonary dysplasia	0.742	0.89	0.46-1.75
Apnea	0.103	2.57	0.83-8.01
ARD	0.006	2.12	0.97-4.63
PVH	0.728	0.83	0.29-2.39
Perinatal asphyxia	0.499	1.49	0.47-4.68
Periventricular leukomalacia	0.725	0.80	0.24-2.72
Feeding intolerance	0.054	1.93	0.99-3.76
IMV	0.228	0.61	0.28-1.36
CPAP	0.547	0.79	0.37-1.69
For each day of use of gastric tube	0.124	1.03	0.99-1.06
Enteral intake pre-symptoms ≥147 mL/kg/day*	0.044	0.36	0.14-0.98
Surfactant	0.209	1.61	0.77-3.38
Caffeine	0.440	1.42	0.58-3.47
Opioid	0.241	1.52	0.75-3.08
Dopamine	0.622	0.85	0.46-1.60
Prenatal steroid	0.565	1.20	0.65-2.23
Postnatal steroid	0.018	0.32	0.12-0.82
Bronchodilator	0.186	0.62	0.31-1.25

OR = odds-ratio for GERD; CI = confidence interval; GA = gestational age;
SGA = small for gestational age; ARD = acute respiratory distress in the first week of life; PVH = periventricular and ventricular hemorrhage grade III, IV;
IMV = intermittent mandatory ventilation; CPAP = continuous positive airway pressure
* P75 value of sample

TABLE 3. Multivariate logistic regression analysis (n = 174), excluding the symptoms suggestive of DRGE, adjusted for the birthweight and postconceptional age at time of pH study

Variable	*P*-value	OR	95% CI
ARD	0.022	2.51	1.14-5.51
Postnatal steroid	0.008	0.26	0.10-0.70

ARD = acute respiratory disease in the first week of life

pre-symptom enteral volume ≥147 mL/kg/day were identified as protective factors (Table 2).

The variables used in the multivariate logistic regression were those with a *P*-value <0.25 in the univariate analysis (Table 2). We obtained distinct results in two models. When symptoms were carried on in multivariate analysis the set of variables that better defined the risk of IR ≥10% were the following: vomiting OR = 3.29 (IC95% 1.62-6.71), *P* = 0.001; regurgitations OR = 4.94 (IC95% 1.89-12.96), *P* = 0.001 and apnea OR = 4.28 (IC95% 1.19-15.43), *P* = 0.026. When symptoms were excluded of the multivariate analysis ARD was identified as a risk factor and postnatal use of steroid remained in the model as protective variable for RI ≥10% (Table 3).

The duration of hospitalization and weight at discharge from hospital were similar in the two groups: 69.1 ± 26.2 days and 2413 ± 457 grams, respectively, in the cases versus 74.7 ± 28.4 days (*P* = 0.099) and 2332 ± 414 g (*P* = 0.422) in the controls.

DISCUSSION

This paper evaluated a large number of preterm infants with clinical manifestations suggestive of GERD with high RI values (mean 21.6%% ± 9.6%) and identified symptoms, demographic variables and factors related to intensive care that were associated with RI ≥10% either independent or as part of a set of variables.

Diagnosis of GERD in premature infants is hampered by various aspects, specially the lack of well-defined clinical and laboratory parameters. Esophageal pH monitoring is far from routine in neonatal units[8, 36] and a definition of normal values of RI remains to be established. Therefore, the threshold value for the RI varies from one author to another (>5%–15%)[1, 7]. In this study, an RI ≥10% was adopted as in other studies[12] and corresponds to the 90th percentile in term infants[34]. The mean of RI achieved here were similar to other recent papers[26, 27].

DRGE has presented low incidence in preterms[1, 11] so the use of case-control study is more efficient than prospective studies. The selection of a control group is a critical issue in case control studies. Unhealthy preterms with clinic manifestations suggestive of GERD were selected. The use of infants without reflux-like symptoms may establish a systematic difference related to exposure between the groups and distort the odds-ratio. So, the two groups were similar in respect to the majority of the variables studied. However, mean birthweight was significantly lower in the controls and the PCA at pH study was younger in the cases. Therefore, to eliminate a possible confounding effect, regression analysis was adjusted according to the two variables.

The authors who have suggested a causal relationship between GER and apnea in preterm infants have emphasized the importance of associated digestive manifestations in these patients[13, 20, 21]. In fact, this study found that digestive manifestations were more common (3-5 times) in cases (IR ≥10%) than in the controls (IR <10%). Those results were confirmed by multivariate analysis where apnea, vomiting and regurgitations all together define the risk for IR ≥10%. This result does not allow us to accept or reject the hypothesis of causality between GER and apnea. Although there is a physiological substrate that explains the relationship between GER and apnea[33] it is believed that in the majority of cases, apnea and GER merely coexist in premature infants as manifestations of immaturity with no causal relationship between them[21, 31].

Female gender was associated with high RI. The authors disagree that in adults the association between DRGE and gender may occur, but there are descriptions of predominance of DRGE in females[22]. Emotional status and ingestion of particular foods were implicated[22] but hormonal influences may not be disregarded. Gender association with greater esophageal acid exposure have been reported in caucasian female infants[24].

Another result that has also not been previously reported is postnatal corticoid as a protective factor for increased IR. This result may be associated with a greater number of infants with BPD among controls. In this study, in the various models of multivariate analysis either, adjusted or not for the variable BPD, the OR for postnatal corticoid use remained strongly significant. Prenatal use of corticoid is known to be related to maturation of the intestinal motor pattern in premature infants[23] and has been related to an increase in GERD[6]. Inversely, no effect of postnatal corticoid on gastrointestinal motility has been previously described. Therefore, further studies are required to evaluate the possible effects of prenatal and postnatal corticoids in GERD.

We investigated the effect of the volume of feedings prior to the onset of symptoms, since great volumes are important determinants of episodes of reflux[7, 35]. In addition, we observed that the cases had an onset or deterioration in apnea and desaturations as the volume of feedings increased, although this association was not specific for GERD[5]. Unexpectedly, a volume ≥147 mL/kg/day pre-symptoms was found to be a protective factor for the occurrence of increased RI, meaning that the control group tolerated the increase in feeding volume better than the study group. The 30 infants who showed symptoms only when the volume of enteral intake was ≥147 mL/kg/day, 67% were controls and 33% cases. The volume of the feeding immediately preceding the onset of symptoms was significantly lower in the cases. Nevertheless, the OR for GERD with lower feeding volumes (values corresponding to the P25, P25-P75 of sample) was not significant.

The exclusion of symptoms of the multiple analysis makes feasible the expression of another two variables that define the chance of RI ≥10%. Together with postnatal corticoid, the respiratory insufficiency was identified as a factor that increases the chance (OR = 2.51) of IR ≥10%. This result agrees with the previous anecdotal reports that respiratory distress syndrome during the first week of life is associated with a diagnosis of GERD[13, 16, 17]. In addition, there is recent evidence that preterm infants with respiratory distress syndrome on mechanical ventilation are at risk of pulmonary aspiration since the first days of life[10].

The use of a gastric tube triggers almost twice the number of reflux episodes in preterm infants[30]. In this study neither the frequency nor duration of use of the gastric tube was associated with greater esophageal acid exposition. Likewise, caffeine, traditionally considered to be a risk factor for GERD, was not relevant in this study, in agreement with data already published by other investigators[2, 7, 26]

BPD has been frequently considered a risk factor for GERD[13, 16] and its presence in these patients ranges from 18.4%–63.0%[1, 15]. In our study, no association was found between BPD and RI ≥10%. These findings agrees with data published by other investigators[1, 17] and allow us to speculate that the greater frequency of diagnosis of GERD in premature infants with BPD may occur as a result of the greater frequency of ARD in these patients, in the first week of life.

One limitation of this study is the absence of information regarding the racial constitution of the sample. In both children and adults, GERD affects predominantly caucasians[24]. A further limitation is the small sample of patients with serious neurological impairments. Such children are known to have a high incidence of GERD[16].

GERD in newborn infants has been associated with longer hospital stays[11] and higher costs. The duration of hospital stay was similar in both groups, probably due to the early diagnosis and initiation of conservative treatment (posture and dietary management).

In conclusion, this study found that vomiting and regurgitation, apnea, female gender, and respiratory failure in the first days of life were variables predictive of increased RI and feasible GERD in preterm infants with birthweight <2000 g. These findings may be helpful in clinical management and may allow selection of more appropriate sample populations for future clinical research trials.

ACKNOWLEDGMENTS

The authors would like to express their deep gratitude to Helymar da Costa Machado of the Statistics Department of the Research Commission for the statistical analysis.

Mezzacappa MA, Rosa AC. Preditores clínicos para pHmetria esofágica anormal em prematuros. Arq Gastroenterol. 2008;45(3):234-8.

RESUMO - ***Racional*** - Os fatores de risco para a doença pelo refluxo gastroesofágico em recém-nascidos prematuros não foram, até momento, claramente estabelecidos. **Objetivo** - Identificar fatores associados ao aumento da exposição ácida intra-esofágica em prematuros durante o período de internação em unidade neonatal. ***Métodos*** – Realizou-se estudo de caso controle com prematuros que realizaram monitorização prolongada do pH esofágico por suspeita clínica de doença do refluxo. Foram selecionados 87 recém-nascidos com valor do índice de refluxo (percentual do tempo total do exame com pH abaixo de 4) ≥10% (casos) e 87 recém-nascidos com índice de refluxo <10% (controles). Casos e controles não foram emparelhados. As variáveis estudadas foram as demográficas, os sinais e sintomas clínicos, os principais diagnósticos e alguns aspectos da terapêutica. Foram utilizadas as análises de regressão logística uni e multivariada, ambas ajustadas pelo peso ao nascimento e pela idade pós-conceptual no momento do estudo de pH. ***Resultados*** - Os fatores que se associaram a maior chance de índice de refluxo ≥10% foram: vômitos, regurgitações, apnéia, sexo feminino e insuficiência respiratória na 1ª semana de vida. As variáveis que se associaram a menor freqüência de índice de refluxo <10% foram: volume de mamada ao início dos sintomas ≥147mL/kg/d e uso de corticóide pós-natal. ***Conclusões*** - Vômitos, regurgitações, apnéia, sexo feminino e a insuficiência respiratória na primeira semana de vida foram variáveis preditoras para elevada exposição ácida do esôfago em prematuros com peso ao nascer <2000 g. A displasia broncopulmonar e o uso de cafeína não se associaram ao índice de refluxo ≥10%.

DESCRITORES – Refluxo gastroesofágico. Determinação da acidez gástrica. Fatores de risco. Prematuro.

REFERENCES

1. Akinola E, Rosenkrantz TS, Pappagallo M, Mckay K, Hussain N. Gastroesophageal reflux in infants < 32 weeks gestational age at birth: lack of relationship to chronic lung disease. Am J Perinatol. 2004;21:57-62.
2. Ariagno RL, Kikkert MA, Mirmiran M, Conrad C, Baldwin RB. Cisapride decreases gastroesophageal reflux in preterm infants. Pediatrics. 2001;107:e58.
3. Ballard JL, Khoury JC, Wedig K, Wang L, Eilers-Walsman BL, Lipp R. New Ballard Score, expanded to include extremely premature infants. J Pediatr. 1991;119:417-23.
4. Battaglia FC, Lubchenco LO. A practical classification of newborn infants by weight and gestational age. J Pediatr. 1967;71:159-63.
5. Blondheim O, Abbasi S, Fox WW, Buthani VK. Effect of enteral gavage feeding rate on pulmonary functions of very low birth weight infants. J Pediatr. 1993;122(5 Pt 1): 751-5.
6. Chin SO, Brodsky NL, Bhandari V. Antenatal steroid use is associated with increased gastroesophageal reflux in neonates. Am J Perinatol. 2003;20:205-13.
7. Davidson G. The role of lower esophageal sphincter function and dysmotility in gastroesophageal reflux in premature infants and in the first year of life. J Pediatr Gastroenterol Nutr. 2003;37 (Suppl 1):s17-22.
8. Dhillon AS, Ewer AK. Diagnosis and management of gastro-oesophageal reflux in preterm infants in neonatal intensive care units. Acta Paediatr. 2004;93:88-93.
9. Donohue PK, Baker SF, Allen MC. Duration of apnea and bradycardia in VLBW infants [abstract]. Pediatrics. 1997;100 (Suppl):496.
10. Farhath S, Aghai ZH, Nakhla T, Saslow J, He Z, Soundar S, Mehta DI. Pepsin, a reliable marker of gastric aspiration, is frequently detected in tracheal aspirates from premature ventilated neonates: relationship with feeding and methylxantine therapy. J Pediatr Gastroenterol Nutr. 2006;43:336-41.
11. Frakaloss G, Burke G, Sanders MR. Impact of gastroesophageal reflux on growth and hospital stay in premature infants. J Pediatr Gastroenterol Nutr. 1998;26:146-50.
12. Grant L, Cochran D. Can pH monitoring reliably detect gastro-oesophageal reflux in preterm infants? Arch Dis Child Fetal Neonatal Ed. 2001;85:F155-F7.
13. Herbst JJ, Minton SD, Book LS. Gastroesophageal reflux causing respiratory distress and apnea in newborn infants. J Pediatr. 1979;95 (Pt 1):763-8.
14. Hosmer DW, Lemeshow S. Applied Logistic Regression. New York: John Wiley; 1989.
15. Hrabovsky EE, Mullett MD. Gastroesophageal reflux and the premature infant. J Pediatr Surg. 1986;21:583-7.
16. Jadcherla SR. Gastroesophageal reflux in the neonate. Clin Perinatol. 2002;29: 135-58.
17. Khalaf MN, Porat R, Brodsky NL, Bhandari V. Clinical correlations in infants in the neonatal intensive care unit with varying severity of gastroesophageal reflux. J Pediatr Gastroenterol Nutr. 2001;32:45-9.
18. Kimball AL, Carlton DP. Gastroesophageal reflux medications in the treatment of apnea in premature infants. J Pediatr. 2001;138:355-60.
19. López-Alonso M, Moya MJ, Cabo JA, Ribas J, del Carmen Macías M, Silny J, Sifrim D. 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- e308.
20. Menon AP, Schefft GL, Thach BT. Apnea associated with regurgitation in infants. J Pediatr. 1985;106:625-9.
21. Molloy EJ, Di Fiore JM, Martin RJ. Does gastroesophageal reflux cause apnea in preterm infants? Biol Neonate. 2005;87:254-61.
22. Moraes-Filho JP, Chinzon D, Eisig JN, Hashimoto CL, Zaterka S. Prevalence of heartburn and gastroesophageal reflux disease in the urban Brazilian population. Arq Gastroenterol. 2005;42:122-7.
23. Morriss FH Jr, Moore M, Weisbrodt NW, West MS. Ontogenic development of gastrointestinal motility: IV. Duodenal contractions in preterm infants. Pediatrics. 1986;78:1106-13.
24. Nazer D, Thomas R, Tolia V. Ethnicity and gender related differences in extended intraesophageal pH monitoring parameters in infants: a retrospective study. BMC Pediatrics. 2005;5:24
25. Newell SJ, Booth IW, Morgan ME, Durbin GM, McNeish AS. Gastro-oesophageal reflux in the preterm infants. Arch Dis Child. 1989;64:780-6.
26. Omari TI, Barnett CP, Benninga MA, Lontis R, Goodchild L, Haslam RR, Dent J, Davidson GP. Mechanisms of gastro-oesophageal reflux in preterm and term infants with reflux disease. Gut. 2002;51:475-9.
27. Omari TI, Haslam RR, Lundborg P, Davidson GP. Effect of omeprazole on acid gastroesophageal reflux and gastric acidity in preterm infants with pathological acid reflux. J Pediatr Gastroenterol Nutr. 2007;44:41-4.
28. Orenstein SR. Tests to assess symptoms of gastroesophageal reflux in infants and children. J Pediatr Gastroenterol Nutr. 2003;37(Suppl 1):s29-32.
29. Peter CS, Sprodowski N, Bohnhorst B, Silny J, Poets CF. Gastroesophageal reflux and apnea prematurity: no temporal relationship. Pediatrics. 2002;109:8-11.
30. Peter CS, Wiechers C, Bohnhorst B, Silny J, Poets CF. Influence of nasogastric tubes on gastroesophageal reflux in preterm infants: a multiple intraluminal impedance study. J Pediatr. 2002;141:277-9.
31. Poets CF. Gastroesophageal reflux: a critical review of its role in preterm infants. Pediatrics. 2004;113:e128-32.
32. Shennan AT, Dunn MS, Ohlsson A, Lennox K, Hoskins EM. Abnormal pulmonary outcomes in premature infants: prediction from oxygen requirement in the neonatal period. Pediatrics. 1988;82:527-32.
33. Thach BT. Reflux associated apnea in infants: evidence for a laryngeal chemoreflex. Am J Med. 1997;103:120s-4s.
34. Vandenplas Y, Goyvaerts H, Helven R, Sacre L. Gastroesophageal reflux, as measured by 24-hour pH monitoring, in 509 healthy infants screened for risk of sudden infant death syndrome. Pediatrics. 1991;88:834-40.
35. Vandenplas Y, Hassall E. Mechanisms of gastroesophageal reflux and gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr. 2002;35:119-36.
36. Ward RM, Lemons JA, Molteni RA. Cisapride: a survey of the frequency of use and adverse events in premature newborns. Pediatrics. 1999;103:469-72.

Recebido em 13/6/2007.
Aprovado em 15/8/2007.