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ORIGINAL ARTICLE

Elimination Diet versus Medical Treatment Interventions in Management of Infants with Gastroesophageal Reflux

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ABSTRACT

Keywords: GERD; GER; CoMiSs; Cow's Milk, CMPA

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Background: Gastroesophageal reflux is the passage of the gastric contents into the esophagus, with or without regurgitation and/or vomiting. In children, a therapeutic trial with antacid medication is advised for early management. **Objectives:** We aimed to compare the effect of cow's milk protein eliminated diet versus various medical treatments in management of infant reflux. **Methodology:** This single-blinded randomized controlled trial study included 300 infants presented with manifestations of GERD presented to outpatient clinic of pediatrics department at Aswan University Hospital in the period from January 2021 till December 2022. **Results:** The relationship between Cow's Milk-related Symptom Score (CoMiSS) results and improvement of GERD symptoms in groups V and IV, most cases with CoMiSS positive (89% and 87.5%) showed improvement and the CoMiSS negative cases showed minimal improvement (12.5% and 7.1%). On the other hand, for cases in group III, improvement was higher in CoMiSS negative cases (53%) compared with CoMiSS positive cases only 6.7%,. Contrarily, among Groups I and II, rate of improvement was higher among CoMiSS negative patients (22% and 65 %) compared with CoMiSS positive only (5% and 12%). **Conclusion:** CoMiSS Score is a simple, fast, and easy-to-use useful tool for screening infants presented with GERD symptoms.

INTRODUCTION

Gastroesophageal reflux (GER) is the passage of the gastric contents into the esophagus, with or without regurgitation and/or vomiting. This definition according to the latest guidelines from the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN), published in 2018 **(1)**. GER is considered a normal, physiological process, it may represent a pathological condition named gastroesophageal reflux disease (GERD), when it causes symptoms or complications that are associated with significant

morbidity. Epidemiological studies suggested that GER occurs in approximately 50% of infants < 2 months of age, 60–70% of infants 3–4 months, and 5% of infants by 12 months of age **(2)**.

GER and GERD may cause heightened parental anxiety and stress and may have an adverse effect on quality of life of the child as well as the parent **(3)**. Several studies have shown that there is a subgroup of infants with cow's milk protein allergy (CMPA) who presented with regurgitation and vomiting: symptoms that are indistinguishable from GER. Some authors suggest that the two conditions may be causally related **(4)**. The overlap between gastrointestinal (GI) manifestations of CMPA and frequent (functional) GI complaints such as GER(D) is a consequence of the fact that objective diagnostic criteria for each of the entities are missing. Although it has been estimated that the prevalence of GERD attributable to CMPA is as high as 56%, this association is not scientifically proven **(5)**.

Clinical presentations vary with age. Although GER is often present at birth, regurgitation may not be pronounced until the 2nd or 3rd week of life when the oral intake is increased with a peak at 4 months of age **(1 & 6)**. In addition to regurgitation, infants and young children with GERD may present with irritability, feeding refusal, gagging, failure to thrive, sleep disturbance, chronic cough, wheezing, stridor, and torticollis **(7)**.

None of the signs and symptoms of GER and GERD are specific and there is no gold standard diagnostic test/tool. Differential diagnosis is broad and includes pyloric stenosis, hiatal hernia, intestinal malrotation, intussusception, food allergy, food intolerance, achalasia, gastritis, gastroparesis, eosinophilic esophagitis, peptic ulcer, sepsis, congenital adrenal hyperplasia, increased intracranial pressure, metabolic acidosis, and inborn error of metabolism **(8)**.

Regurgitation/vomiting onset after 6 months of age, increasing persisting regurgitation/vomiting > 1 year of age, consistently forceful vomiting, bilious vomiting, fever, lethargy, significant weight loss, excessive irritability, hematemesis, difficulty swallowing, abdominal distension or tenderness, constipation, melena, hematochezia, chronic diarrhea, seizures, hypo/hypertonia, bulging fontanelle, micro/macrocephaly, abnormal neurologic findings, and hepatosplenomegaly suggest a diagnosis other than GERD **(9)**.

Respiratory complications include reactive airway disease, sinusitis, laryngitis, recurrent aspiration pneumonia, and apparent life-threatening events **(7)**. Biomarkers, such as salivary pepsin, have not been shown to be useful to diagnose GERD. Pepsin can be found in the mouth of almost one-third of control patients **(10)**.

Regarding the association between GERD and CMPA there are several studies were performed with controversial results on prevalence of CMPA in infants with GER **(11)**. This current study was performed for the first time in our region to investigate the co-existence of CMPA in a group of infants with GERD. In these cases, the possibility of GERD caused by CMPA would be excluded without using unnecessary medications. Nutritional management is recommended as a first-line approach in infants, while in children, a therapeutic trial with antacid medication is advised for early management **(12)**.

The current study aims are:

- To compare the effect of cow's milk protein eliminated diet versus various medical treatment interventions in management of infant reflux.
- To evaluate the effect of cow's milk protein elimination on improvement of infants presented with reflux.

PATIENTS AND METHODS

This single-blinded randomized controlled trial (RCT) study included 300 infants presented with manifestations of GERD presented to the outpatient clinic of pediatrics department at Aswan University Hospital in the period from January 2021 till December 2022. Sample size was calculated using G*Power 3 software **(13)**, with a power of 95% and type I error of 5% (α=0.05 and β=95%) on two tailed test, the minimum required sample was 300 participants (divided into five equal groups, 60 patients are required in each group to detect an effect size of 0.2 in the percentage of positive CoMiSS score.

Full term infant, aged 1 month to 1 year, with manifestations of GER(D) according to the (NASPGHAN) and the (ESPGHAN) definition were included. On the other hand, infants with suggestive metabolic, neurologic or any chronic illness, with previous NICU admission, with genetic, chromosomal disorder or any dysmorphic features, proved gastrointestinal disease or malformation were excluded from the study.

The sample was randomly assigned to five equal (n=60) groups: **Group I**: received prokinetic medication, Domperidone with the newly recommended dose, 200-400 microgram/kg/dose, 3-4 times a day, **Group II:** received a proton pump inhibitor (PPI) medication appropriate for age, esomeprazole 1–2 mg/kg/day administered 30–60 min. before a feeding once daily ,supplied as 10mg powder per a packet for preparation of delayed-release oral suspensions (one sachet dissolved in 20 ml distilled sterile water). **Group III**: received formula thickener without alternation of its nutrient and/or caloric contents (anti-regurgitation (AR) formula). **Group IV:** included bottle fed infants received an appropriate formula that nutritionally balanced and based on amino acids as a protein source. **Group V:** included breast fed infants who exposed to strict cow's milk protein elimination from maternal diet. There is only one primary factor under consideration in the experiment (presentation with possible GERD diagnosis). Similar test subjects are grouped into blocks. Each block is tested against all treatment levels of the primary factor at random order. This is intended to eliminate possible influence by other extraneous factors. All guardians of eligible cases presented were briefly informed about the study during the visit. If interested, they are then informed in detail by the study physician and inclusion and exclusion criteria are verified. For each patient recruited into the study, written informed consent is essentially signed by the guardian prior to inclusion into the study after extensive information about the intent of the study, the study regimen. The investigator will not undertake any diagnostic measures specifically required for the clinical trial until valid consent has been obtained. Upon written informed consent, the patient is scheduled for the baseline visit.

After completion of the baseline assessment, the participant was randomly allocated to one of the five intervention groups. Allocation is done by the biometrician based on a predetermined list generated with a blocked randomization SPSS procedure with a fixed block size. To prevent possible bias, study personnel involved in the recruitment and the baseline assessment do not have access to the randomization lists and are not aware of the block size.

Procedure

All studied infants were subjected to: Full history tacking. Full clinical examination including anthropometric measures with detailed recording of growth rate in addition to any manifestation of faltering growth during the period of study. CoMiSS scoring as an indicator for suspension of CMPA conducted for all studied infants at both first visit and re-done on third visit after one month of exposure to any line of management included in our study. All groups were evaluated initially regarding anthropometry, manifestation of gastroesophageal reflux and CoMiSS scoring. Further re-evaluation, CoMiSS scoring was re-done on the 3rd visit after a month of treatment.

Symptom	Score			
Crying	0	≤1 h/day		
	1	1 to 1.5 h/day		
	2	1.5 to 2 h/day		
	3	2 to 3 h/day		
	4	3 to 4 h/day		
	5	4 to 5 h/day		
	6	≥5 h/day		
Regurgitation	0	0 to 2 episodes/day		
	1	≥3 to ≤5 episodes of small volume		
	2	>5 episodes of >1 coffee spoon		
	3	>5 episodes of ±half of the feedings in< half of the feedings		
	4	continuous regurgitations of small volumes >30 min after each feeding		
	5	regurgitation of half to complete volume of a feeding in at least half of the feedings		
	6	regurgitation of the complete volume after each feeding		
Stools (Bristol scale)	4	type 1 and 2 (hard stools)		
	0	type 3 and 4 (normal stools)		
	2	type 5 (soft stool)		
	4	type 6 (liquid stool, if unrelated to infection)		
	6	type 7 (watery stools)		
Skin symptoms	0 to 6	Atopic eczema	Head-neck-trunk	Arms-legs-hands-feet
		Absent	0	0
		Mild	1	1
		Moderate	2	2
		Severe	3	3
	0 to 6	Urticaria (0: no, 6: yes)		
Respiratory symptoms	0	no respiratory symptoms		
	1	slight symptoms		
	2	mild symptoms		
	3	severe symptoms		

CoMiSS Scoring System Score

Statistical analysis

The collected data were verified, coded by the researcher, and analysed using the Statistical Package for Social Sciences **(14)**. Descriptive statistics: Means, standard deviations, medians, ranges, and percentages were calculated.

Test of significances: The Chi-square test was used to compare the difference in distribution of frequencies among different groups. The Shapiro-Wilk test will be used to test for data normality. The student t-test test was calculated to test the mean differences in continuous variables between groups. Multivariable logistic regression analysis was calculated to investigate the significant predictors of steroid sensitivity (Odds Ratio -OR-, 95% confidence interval -95% CI- and Likelihood Ratio Test –LRT). For continuous variables with more than two categories; Two-way ANOVA test was calculated to test the mean differences of the data that follow normal distribution and had repeated measures (between groups, within groups and overall difference), post-hoc test was calculated using Bonferroni corrections for pairwise comparisons between the two study groups. Paired sample t-test test was calculated to test the mean differences in continuous variables within group. A p-value < 0.05 was considered significant.

Ethical considerations

Approval for this study was obtained from Institutional review board (IRB No. Asw24356) of Faculty of Medicine, Aswan University hospital prior to study execution. In addition, all participants/caregivers received a written consent form. The informed consent was clear and indicated the purpose of the study, and their freedom to participate or withdraw at any time without any obligation. Furthermore, participants' confidentiality and anonymity were assured by assigning each participant with a code number for the purpose of analysis only. The study was not based on any incentives or rewards for the participants and was abided by the guidelines of Helsinki Declaration **(15)** and the STROBE guidelines **(16)**.

RESULTS

The age of these patients ranged from 1 to 11.5 months old **(Fig. 1)**. The maternal age ranged from 14 to 42 years old with a mean of 25 ± 4.7 and a median of 24 years. Also, patient's weight had a mean of 5.7 ± 1.5 kg with a median of 5.5 (3-11.5 kg). Likely, patient's Length had a median of 57.5 (44-76 cm) with a mean of 58.6 ± 6.9 cm **(Table 1)**.

Distribution of GERD symptoms among cases were illustrated in **table 2 and fig. 2**. The most common symptom was spitting in 95% of cases, crying in 83%, vomiting in about three-quarters, respiratory manifestations in 57%, growth faltering in 55%, diarrhea in 40%, skin manifestation in 34% and constipation in 7%. According to the patient's signs, respiratory manifestation was reported in 59%, skin manifestation in 32% and growth faltering in 50%.

The distribution of GERD demographic and birth risk factors was illustrated in **table 3**. The groups were matched for age (p=0.215), however, group I cases were significantly (p=0.026) younger when categorizing patients into age group i.e., two-thirds of groups I aged 0-3 months compared with other groups (Fig. 18). As well, cases were matched for sex (p=0.533) and maternal age (p=0.972) and weight of cases (p=0.101). Moreover, there was significant association between length of patient and treatment group (p<0.001). Group I case had lower mean length (55.5 ± 6.4 cm) compared with group III (60.1 ± 7.2 cm, p<0.001), group IV (60.5 ± 6.1 cm, p<0.001) and group V (59.5 ± 7.2 cm, p=0.001). Likewise, patients of group II were shorter (57.5 ± 6.8 cm) compared with group III (p=0.042) and group IV (p=0.019).

The distribution of clinical manifestations was illustrated in **table 4**. Percentage of cases with spitting was significantly (p=0.009) lower in group II (85%) than the other groups (95% to 98.3%). Likewise, percentage of cases with vomiting was significantly (p=0.039) lower in group I (61.7%) than the other groups (73.3% to 86.7%). Groups were matched for all other symptoms and signs. Notably, improvement was evident in groups IV and V (51.7%) followed by group III (45%), group II (30%) and least in group I (16.7%). This difference was statistically significant (p<0.001) (Fig. 20). Additionally, groups were comparable for the frequency of positive CoMiSS score (≥ 12 points) at baseline (p=0.069). On the other hand, at the 3rd visit, percentage of cases with positive CoMiSS score were significantly higher in groups I and II (32% and 37%) followed by group III (27%), group IV (5%) and no cases in in group V (0%). This difference was statistically significant (p<0.001) **(Fig. 3)**.

The relationship between CoMiSs Results and improvement of GERD symptoms was presented in **table 5**. For groups V and IV, most cases with CoMiSs positive (89% and 87.5%) showed improvement in GERD symptoms and the CoMiSs negative cases showed minimal improvement (12.5% and 7.1%). On the other hand, for cases in group III, improvement was higher in CoMiss negative cases (53%) compared with CoMiSs positive cases (6.7%), and this was statistically significant (p=0.001). Contrarily, among Groups I and II, rate of improvement was higher among CoMiSs negative patients (22% and 65%) compared with CoMiSs positive only (5% and 12%). These differences were significant (p<0.001).

DISCUSSION

GER is a condition that mostly affects the esophagus, and it is one of the most frequent complaints in centers of pediatrics and pediatric gastroenterology **(9)**. The Rome IV criteria has defined Infant regurgitation as functional gastrointestinal disorders (FGIDs) of infancy that must include at least due episodes of regurgitation per day for at least three weeks in an otherwise healthy infant 3 weeks to 12 months of age without retching, hematemesis, aspiration, apnea, failure to thrive, feeding or swallowing difficulties or abnormal posturing **(17)**.

This study included 300 infants presented with manifestations of GER (D) according to the (NASPGHAN), the (ESPGHAN) definition and The Rome IV criteria in addition to Infant GERD Questionnaire Revised. Recently CoMiSs was modified in which a score of more than 10 in infants supported a diagnosis of CMPA. The stool pattern was also changed from the Bristol Stool Scale to the Brussels Infant and Toddlers Stool Scale as a more user-friendly tool for non-toilet trained children **(18)**.

Regarding the age, in the current study and among the studied cases GERD dominantly prevalent at age group (1-3 Month). This is more or less with Dranove (2008) **(6)** and Vandenplas et al. (2018) **(9)** who reported that epidemiological studies suggest that gastroesophageal reflux occurs in approximately 50% of infants younger than 2 months of age, 60–70% of infants 3–4 months of age, and 5% of infants by 12 months of age, and also with Zeevenhooven et al. (2017) **(19)** who reported that infant regurgitation is the most common functional gastrointestinal disorders (FGID) in infants (<12 months of age) with reported prevalence rates ranging from 8-26% in this age group at the peak age around 2-4 months, prevalence rates have been reported to be as high as 67-87%. However, the prevalence of GER and GERD vary according to the population, the study design and the diagnostic criteria by the different criteria that have been used to define regurgitation in the past **(20)**.

In this study and in terms of sex distribution, male infants comprised most of all groups, ranging from 45.0% to 58.3%. However, there were no statistically significant differences observed between the groups. this in line with Singendonk et al. (2019) **(21)** who reported that gender was not associated with an increased risk of GER or GERD, similar to what was reported in previous pediatric studies in which the occurrence of pathological pH monitoring data was equally frequent in both sex. However, Chogle et al. (2016) **(22)** reported that It is also interesting to note that male and female infants show a comparable prevalence of FGIDs. Also a study in China found that male gender is a risk factor for GER(D) and he interpreted this as being male, living in a rural area and consumption of formula feeds between 0 and 1 month increased the risk of infant regurgitation while being exclusively breastfed for 4–6 months reduced the risk by 99% Parents in general tend to overfeed while bottle feeding, as they are less likely to respond to child's satiety cues. This is further exacerbated by Chinese cultural practice of feeding higher volumes of milk (>840mls/day) to the male infants **(23)**.

In this study the primary outcomes considered included improvement of GERD clinical symptoms. These were usually assessed through leading questions to the mother and childcare providers and include the following: number of spitting episodes, vomiting episodes, significant crying/fussiness, failure to thrive, respiratory manifestations skin manifestations diarrhea and constipation. In our study spitting/regurgitation was the most frequent complaint this was in line with Leung (2011) **(24)**, who reported that reflux resulted from protozoal diseases mainly manifested by spitting/regurgitation

Regurgitation was the most frequent symptom and is present in nearly all cases. Also Our study comes in accordance with Vandenplas et al. (2017), Vandenplas et al. (2019), Vandenplas and Kindt (2021) **(25-27)** who reported that most common symptoms of GERD in infancy are spitting/ regurgitation and crying/fussiness while vomiting and respiratory manifestation follow them, then growth faltering. In the absence of frequent regurgitation or feeding problems pathological GERD according to pH monitoring results was unlikely (negative predictive value 87–90%) **(5)**. The prevalence of GERD symptoms varies considerably, depending on method of data collection and criteria used to define symptoms **(21)**.

In this study, we considered crying as a significant matter if crying or fussiness lasted at least 3 hours per days, 3 days per week. This agreed with Benninga et al. (2016) **(16)** who estimated that for clinical research purposes, to fulfill the definition of colic these episodes of crying or fussiness should last at least 3 hours per days, for a minimum of one day when measured by a prospectively kept 24 hours behavior diary or 3 days per week according to a caregiver's interview. In this study we found non-GERD symptoms as skin manifestations (eczema & /or urticaria), diarrhea and finally constipation were presented with different rates in significant number of cases the presence of that manifestation may be due to the presence of another pathological factor in addition to GERD.

Cow milk protein allergy is the most common type of food allergy particularly in infancy and childhood **(28)** the prevalence of hospital based diagnosed CMPA in the first year of life ranges from 0.5% to 3% of infants **(5)**. Parents recognize CMPA in their children much more frequently than can be confirmed by diagnostic studies, and symptoms suggesting adverse reactions to cow's milk protein occur in 5% to 15% of children, exceeding true approximations of the prevalence of the CMPA **(29)**.

Regarding the various anti GERD measures used for 6 weeks from the initial visit for every case in this study, we aimed at determining impact of CMP elimination in GERD management either by CMP elimination from maternal diet (group V) or introduction of amino acid-based formula for bottle fed infants (group IV) and exclusion of any dairy products or other foods having cross antigenicity with CMP e.g. soya beans for whom complementary feeding had already been started before inclusion in the study and the impact of other non-surgical modalities of managements named introduction of anti-reguerge (AR) formula for bottle fed infant (group III), the use of PPI (group II) and administration of domperidone as a prokinetic agent (group I).

The mothers who were exposed to CMP elimination from their diet referred to a nutrition specialist to compensate the eliminated food lists with others matched with dairy products eliminations. Non-significant relationship was found between CMP elimination via maternal diet restriction for breast fed infants or introduction of amino acids-based formula for bottle fed infants in progress of GERD symptoms. During the mother's elimination diet, she should receive nutritional counseling and supplements of 1000 mg of calcium per day and 800 IU of vitamin D per day **(30)**. In this study and regarding the outcomes after 6 weeks of interventions of patient symptoms and CoMiSs score, this score was applied on all cases of the study at first visit then 4 weeks later (third visit) and the results regarding GERD symptoms revealed that in groups IV and V where cow's milk protein (CMP) was eliminated, improvement of GERD symptoms was evident (51.7%) followed by group III (45%), group II (30%) and least in group I (16.7%).

This difference was significant and most of the improved cases in groups IV and V are CoMiSs positive, and the majority of the improved cases in groups I, II and III are CoMiSs negative. Re-application of CoMiSs score at third visit revealed a significant decrease in the score points in CoMiSs Positive cases in groups IV and V and minimal changes in the score in other groups who were exposed to another interventions. This support the likelihood of two points, the first point was that there is a causal relationship between GERD and CMP and the second point was that CoMiSs is a valuable tool in suspicion of CMPA diagnosis. In conclusion our study revealed that, there was statistically significant difference in improvement of GERD symptoms between CoMiSs score positive cases and CoMiSs negative cases when exposed to CMP elimination. This in line with Omari et al. (2020) **(31)** who estimated that; the association of CMPA-GERD was reported in 16–56% of cases with persistent gastrointestinal symptoms and suspicion of GERD, irrespective of breast or formula feeding **(31)**.

Strengths and Limitations

Up-to-our knowledge, limited number of studies comparing the CMP elimination with other non-surgical measures for management of Egyptian infants with GERD. This study contains useful new information for decision making in elimination of CMP for GERD management in infancy. This study evaluates the effect of different non-surgical modalities and not only CMP elimination. Stools were analyzed in photographic images and/or by direct visualization in the diapers, this made accurate interpretation of the stool's consistency.

The current study encountered some limitations, in this study, the CoMiSs was not determined of presumed healthy infants in Aswan. Lastly, the current work lacks the application of health education program to the infants' mothers to minimize the incidence of GERD manifestation and to alleviate their quality of life.

CONCLUSION

In conclusion, GERD was found to be the most frequent complaint in health care centers of pediatrics and pediatric gastroenterology. GER is physiological in most infants and needs no tests to be diagnosed. The therapy of pediatric GERD depends upon a combination of conservative, pharmacological and rarely surgical measures. Under- or over-diagnosis of CMPA and GERD are likely to occur. Therefore, CMP elimination diet and treatment with anti-acids are often empirically initiated and are, sometimes, excessively protracted. CoMiSS is a simple and practicable tool for early identification and screening for CMPA as a primary cause for GERD

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Tables

Table (1): Socio-demographic characteristics of the studied cases

Variable	Category	N = 300
Age in months	• **Mean ± SD**	4.21 ± 2.5
	• **Median (Range)**	3 (1 –11.5)
Age Group	• **0 – 3 months**	152 (50.7%)
	• **3 – 6 months**	90 (30%)
	• **> 6 months**	58 (19.3%)
Sex	• **Male**	152 (50.7%)
	• **Female**	148 (49.3%)
Maternal Age/years	• **Mean ± SD**	24.95 ± 4.7
	• **Median (Range)**	24 (14 – 42)
Weight/Kg	• **Mean ± SD**	5.74 ± 1.5
	• **Median (Range)**	5.5 (3 – 11.5)
Length/cm	• **Mean ± SD**	58.62 ± 6.9
	• **Median (Range)**	57.5 (44 – 76)

Table (2): Clinical Data characteristics of the studied cases

Variable	N = 300
GERD Symptoms	
• **Spitting**	285 (95%)
• **Vomiting**	224 (74.7%)
• **Crying**	249 (83%)
• **Chest symptoms**	172 (57.3%)
• **Growth faltering symptoms.**	166 (55.3%)
• **Skin symptoms**	101 (33.7%)
• **Diarrhoea**	121 (40.3%)
• **Constipation**	22 (7.3%)
• **Chest signs**	177 (59%)
• **Skin sings**	95 (31.7%)
• **Growth Faltering sings**	149 (49.7%)
CoMiSS Score Baseline	
• **Mean ± SD**	6.90 ± 6.1
• **Median (Range)**	0 (0 – 25)
CoMiSS Score after 4-weeks	
• **Mean ± SD**	4.47 ± 4.1
• **Median (Range)**	0 (0 – 23)
Improvement of Symptoms	117 (39%)

Table (3): Socio-demographic Differences between the Treatment Groups

	Group I (n = 60)	Group 1I (n = 60)	Group III (n = 60)	Group IV (n = 60)	Group IV (n = 60)	P-value
Age/months	3.67 ± 1.2	4.08 ± 1.4	4.73 ± 1.5	4.26 ± 1.5	4.33 ± 1.6	
P-value**	I vs II= 0.370 I vs III= 0.057	II vs III= 0.149 II vs IV= 0.687	III vs IV= 0.297 III vs V= 0.370	IV vs V= 0.884 IV vs I= 0.194	V vs I= 0.149 V vs II= 0.583	= 0.215*
Age Group						
• **0 – 3 months**	40 (66.7%)	32 (53.3%)	22 (36.7%)	30 (50%)	28 (46.7%)	**= 0.026*****
• **3 – 6 months**	8 (13.3%)	16 (26.7%)	28 (46.7%)	18 (30%)	20 (33.3%)	
• **> 6 months**	12 (20%)	12 (20%)	10 (16.7%)	12 (20%)	12 (20%)	
Sex						
• **Female**	31 (51.7%)	32 (53.3%)	33 (55%)	27 (45%)	25 (41.7%)	= 0.533***
• **Male**	29 (48.3%)	28 (46.7%)	27 (45%)	33 (55%)	35 (58.3%)	
Maternal Age/y	24.93 ± 5.1	25.23 ± 4.7	24.75 ± 3.9	24.73 ± 5.1	25.10 ± 4.5	
P-value**	I vs II= 0.729 I vs III= 0.832	II vs III= 0.567 II vs IV= 0.563	III vs IV= 0.985 III vs V= 0.686	IV vs V= 0.672 IV vs I= 0.813	V vs I= 0.847 V vs II= 0.877	= 0.972*
Weight/kg	5.34 ± 1.3	5.66 ± 1.3	5.04 ± 1.5	5.89 ± 1.5	5.77 ± 1.4	
P-value**	I vs II= 0.231 **I vs III= 0.009**	II vs III= 0.157 II vs IV= 0.388	III vs IV= 0.580 III vs V= 0.309	IV vs V= 0.641 **IV vs I= 0.040**	V vs I= 0.111 V vs II= 0.691	= 0.101*
Length/cm	55.53 ± 6.4	57.52 ± 6.8	60.05 ± 7.2	60.45 ± 6.1	59.53 ± 7.2	
P-value**	I vs II= 0.111 **I vs III< 0.001**	**II vs III= 0.042** **II vs IV= 0.019**	III vs IV= 0.747 III vs V= 0.677	IV vs V= 0.461 **IV vs I< 0.001**	**V vs I= 0.001** V vs II= 0.105	**= 0.001***

*** ANOVA test was used to compare the mean difference between groups**
****Post-hoc test with Bonferroni correction was used for pairwise comparison**
*****Chi-square test was used to compare the percentages between groups**

Table (4): Clinical Data Differences between the Treatment Groups

	Group I	Group 1I	Group III	Group IV	Group IV	P-value*

	(n = 60)	(n = 60)	(n = 60)	(n = 60)	(n = 60)	
Symptoms						
• **Spitting**	59 (98.3%)	51 (85%)	59 (98.3%)	57 (95%)	59 (98.3%)	**= 0.009***
• **Vomiting**	37 (61.7%)	52 (86.7%)	46 (76.7%)	44 (73.3%)	45 (75%)	**= 0.039***
• **Crying**	47 (78.3%)	51 (85%)	55 (91.7%)	45 (75%)	51 (85%)	= 0.127*
• **Chest Manifest.**	30 (50%)	38 (63.3%)	35 (58.3%)	38 (63.3%)	31 (51.7%)	= 0.420*
• **Growth Faltering**	31 (51.7%)	37 (61.7%)	28 (46.7%)	37 (61.7%)	33 (55%)	= 0.393*
• **Skin Manifest.**	19 (31.7%)	16 (26.7%)	20 (33.3%)	20 (33.3%)	26 (43.3%)	= 0.121*
• **Diarrhea**	19 (31.7%)	31 (51.7%)	18 (30%)	26 (43.3%)	27 (45%)	= 0.075*
• **Constipation**	5 (8.3%)	3 (5%)	5 (8.3%)	3 (5%)	6 (10%)	= 0.755*
Signs						
• **Skin Manifest.**	19 (31.7%)	18 (30%)	16 (26.7%)	21 (35%)	21 (35%)	= 0.540*
• **Chest Manifest.**	32 (53.3%)	36 (60%)	x36 (60%)	39 (65%)	34 (56.7%)	= 0.562*
• **Growth Faltering**	30 (50%)	30 (50%)	30 (50%)	30 (50%)	29 (48.3%)	= 0.870*
Positive CoMiss-visit-1	20 (33.3%)	30 (50%)	20 (33.3%)	28 (46.7%)	32 (53.3%)	**= 0.036***
Positive CoMiss-visit-3	19 (31.7%)	22 (36.7%)	16 (26.7%)	3 (5%)	0 (0%)	**< 0.001***
Improvement	10 (16.7%)	18 (30%)	27 (45%)	31 (51.7%)	31 (51.7%)	**< 0.001***

***Chi-square test was used to compare the percentages between groups**

Table (5): Relationship between CoMiss Results and Improvement of GERD Symptoms

	CoMiSs Positive (n=135)		CoMiSs negative (n= 165)		P-value*
	Unimproved (n=85)	Improved (n=50)	Improved (n=52)	Unimproved (n=113)	
Treatment Group					
• **Group V (n=60)**	**28** **3 (10.7%)**	**25 (89.3%)**	**32** **4 (12.5%)**	**28 (87.5%)**	= 0.214
• **Group IV (n=60)**	**32** **4 (12.5%)**	**28 (87.5%)**	**28** **2 (7.1%)**	**26 (92.9%)**	= 0.124
• **Group III(n=60)**	**30** **28 (93.3%)**	**2 (6.7%)**	**30** **16 (53.3%)**	**14 (46.7%)**	**= 0.001**
• **Group II (n=60)**	**25** **22 (88%)**	**3 (12%)**	**35** **23 (65.7%)**	**12 (34.3%)**	**< 0.001**
• **Group I (n=60)**	**20** **19 (95%)**	**1 (5%)**	**40** **9 (22.5%)**	**31 (77.5%)**	**< 0.001**
Total	**76/135 (56.3%)**	**59/135 (43.7%)**	**54/165 (32.7%)**	**111/165 (67.3%)**	

***Chi-square test was used to compare differences in frequency between groups.**

Figures

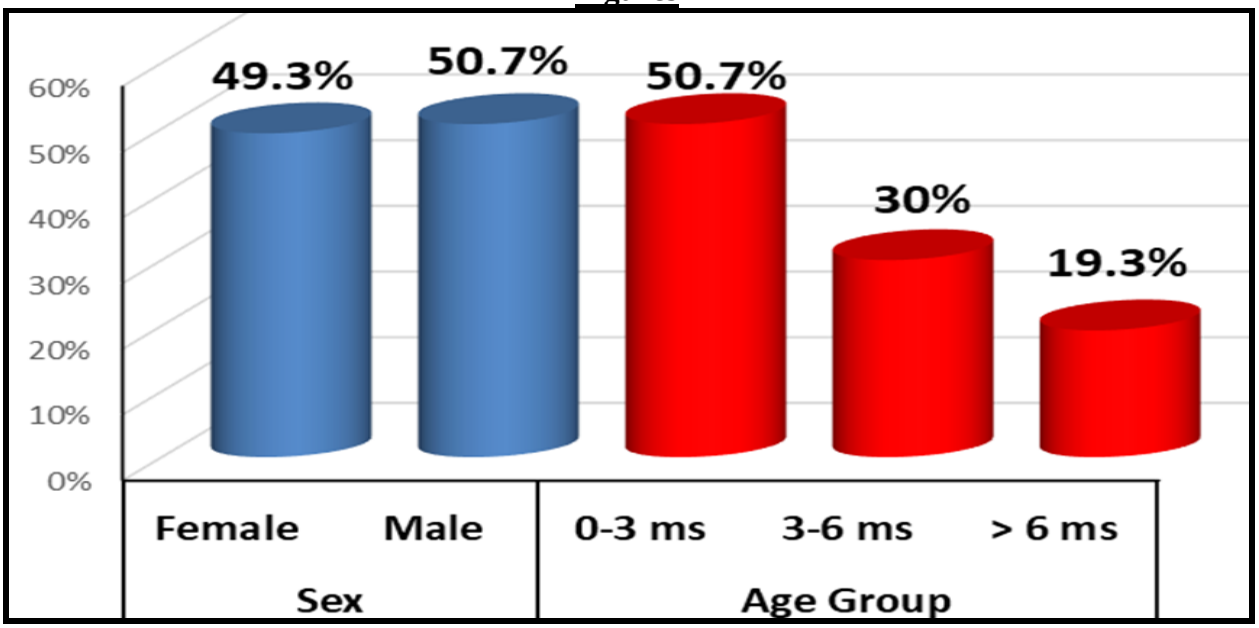

Fig. (1): Sex and Age Group Distribution of the studied cases

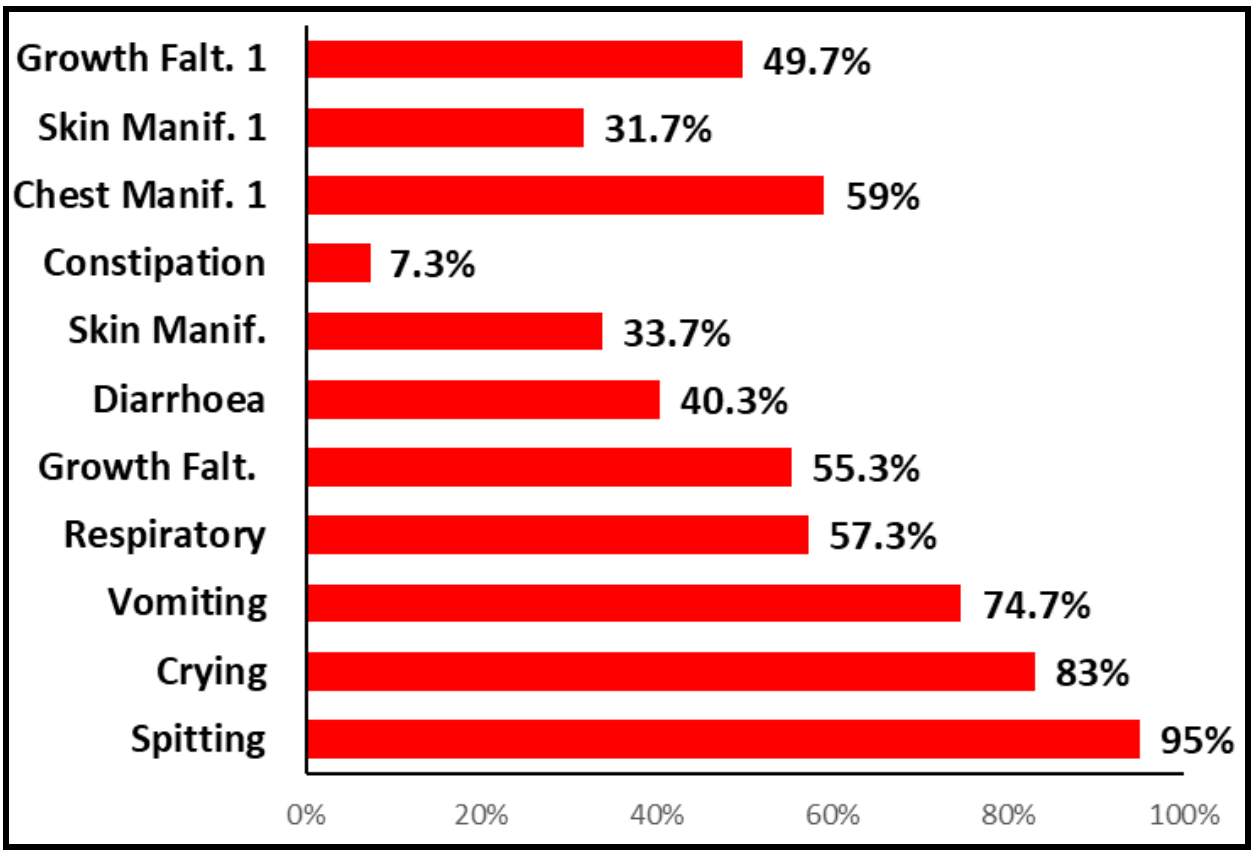

Fig. (2): Prevalence of GERD Symptoms of the studied cases

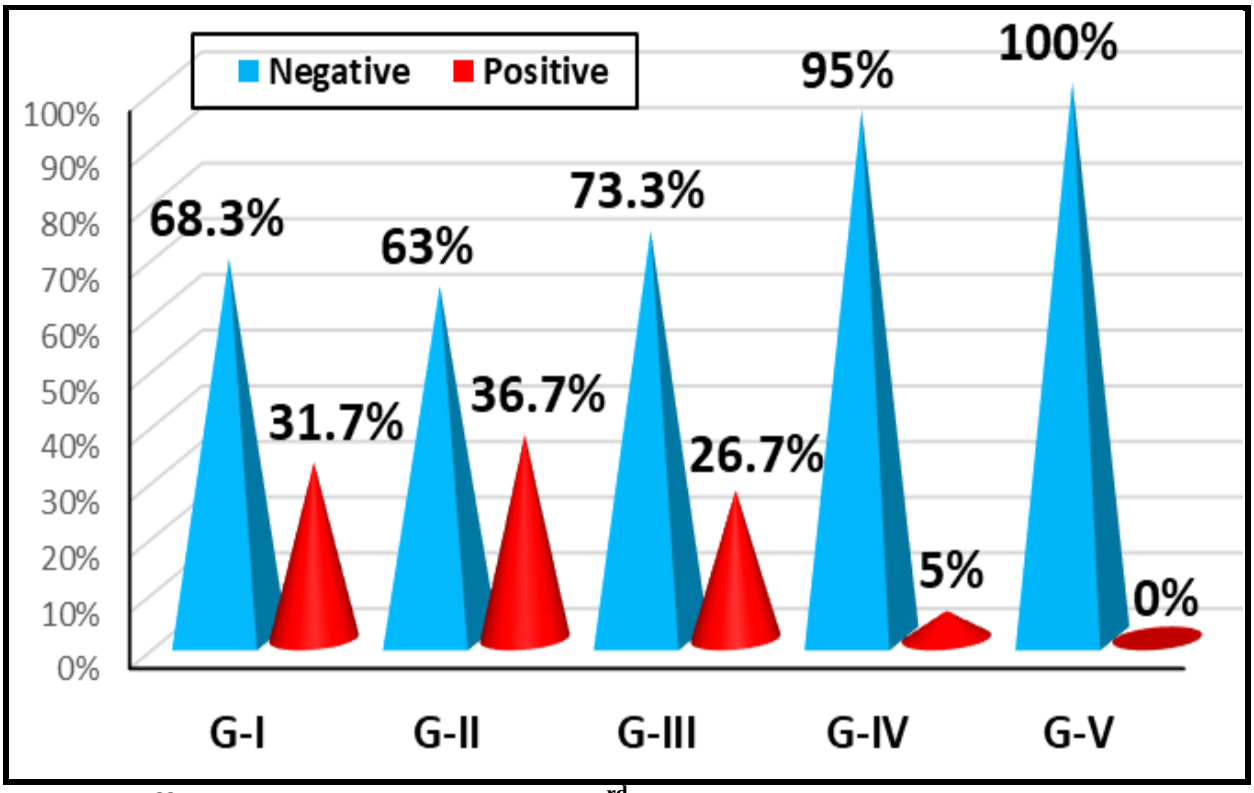

Fig. (3): Difference in the CoMiSs Score at 3rd Visit between Groups