Reviewer’s report

Title: Natural history of gastroesophageal reflux in infancy: new data from a prospective cohort.

Version: 0 Date: 09 Jan 2020

Reviewer: Lisa Mahoney

Reviewer's report:

This study addresses a very important topic - the natural history of reflux in infants. Data in this area is critical to help provide appropriate anticipatory guidance to parents and a foundation for evidence-based decisions for pediatricians and gastroenterologists. The main findings in this study echo previously reported data in this area, namely that reflux is common in infants and improves with time. There are several strengths of this study, including the prospective longitudinal design, the excellent retention of participants throughout the study and the use of a well-established validated survey as the primary outcome measure. The authors also examined a number of additional factors pertinent to the outcome, including risk factors, treatments, growth, etc.

I have a number of comments and suggestions for revisions.

Abstract

1. Page 2, line 34. I would suggest removing exclusion criteria. The authors list a number of additional exclusion criteria in the methods (prematurity, neurologic disorder, surgery, etc), and this abbreviated list in the abstract appears incomplete.

2. Page 2, lines 37-42. The authors define GER and GERD but do not define regurgitation. However, data about prevalence of regurgitation (as distinct from GER and GERD) is presented. Please clarify the definitions for regurgitation.

3. Page 2, line 49. The data do not support the conclusion that pharmacologic agents are justified only for ascertained GERD. While there is an excellent discussion of the risks and benefits associated with pharmacologic therapy for infant GER in the discussion section, the authors only present data on the percentage of children treated in their cohort, not any data on whether this treatment was justified.
Background

1. Page 4, lines 81-83. I would recommend rephrasing this. The 2018 reflux guidelines used the same definition for GERD as the 2009 guidelines.

2. Page 5, line 101. It may be helpful to also note the data from randomized controlled trials showing no difference between PPI and placebo here.

Methods

1. As noted above, GER and GERD are defined, but regurgitation is not. Is regurgitation defined as a score $\geq 1$ on the first item of the I-GERQ-R? If so, I would not expect regurgitation prevalence rates to be any different than the sum of the GER + GERD prevalence rates, as each of these are defined as a score of $\geq 1$ on the first item and either a score of $< 16$ (GER) or $\geq 16$ (GERD). Or is the definition based on parental report on the case-report questionnaire?

2. Please add a more detailed discussion about definitions and specific items collected for all of the secondary outcomes in the parent case report form (e.g. which medications were classified as prokinetics, antacids). Was parent reported data confirmed by chart review, when able (e.g. hospitalization rates and test results)? Alternatively, if not listing specifics in the methods, this could also be presented in a Table 1 containing demographic/baseline data.

Results

1. Page 7, line 161. Please clarify what is meant by "persistently elevated GERD scores". Are these patients who had GERD diagnosed at more than one time point? Or those who carried a diagnosis of GERD beyond 12 months?

2. Risk factors are presented at 1 month and 3 months. Please justify why only these time points were included and not others.

3. Page 8, line 177. Please clarify what is meant by "relevant" treatments.

Discussion

1. There is a large proportion of parents who refused to participate in the study. How does this compare to rates of refusal in other similarly designed birth cohort studies?

2. Page 10, line 223. I would suggest changing this wording to "gender was not associated" rather than "correlated" based on the analysis done.
3. Page 11, lines 246 - 250. This is new data presented in the discussion. This would be more appropriate in the results section.

4. Page 11, line 249. Please clarify what is meant by "prescriptions were unjustified". What criteria were used for justification? Was this solely based on the prescription of PPIs?

5. Page 12, line 294. While I agree with this statement, the data do not support this conclusion. While there is an excellent discussion of the risks and benefits associated with pharmacologic therapy for infant GER in the discussion section, the authors only present data on the percentage of children treated in their cohort, not any data on whether this treatment was justified.

Tables/Graphs

1. There is a significant amount of data listed as collected in the methods that is not presented in the manuscript. I would recommend adding in a Table 1 with baseline demographic data (feeding practices, medication use, growth, hospitalizations, etc).

2. Figure 1: At Q1 timepoints, 140 parents responded, however 141 respondents are listed at the same time point in Table 1.

2. Figure 2 and 3: I would suggest standardizing the Y-axis to 100% for both to allow for easier comparisons.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

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