Peer Review File

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First Round

Reviewer A

Well written and interesting, I enjoyed reviewing it. see below suggestions.
Page 2 line 12: do you think the articles highlighted hematemesis as being a common symptom? I don't think of this as a common symptom of ankyloglossia. Also aspiration and NP regurgitation are not GI symptoms. You could include them as pharyngeal signs of dysphagia and ankyloglossia as a possible etiology?

Reply 1: Thank you for your comments and suggestions. The intention of mentioning hematemesis was to state the general findings within the literature that may have some association to ankyloglossia in infants. See page 2, line 11-12 for our edit.
Changes in the text: "Vomiting and hematemesis were also found to be reported signs in infants with ankyloglossia." Pharyngeal signs were added for consideration in infants with ankyloglossia.

Page 3 Line 7 spell out American Academy of pediatrics for first presentation of AAP

Reply 1: See page 3, line 6 for this change.
Changes in the text: AAP to American Academy of Pediatrics

Page 3 Lines 4-6 - 4 defines as anterior and line 6 defines as anterior or posterior
Reply 1: See page 3, line 6-7
Changes in the text: removed anterior in the original definition of ankyloglossia

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Page 7 line 12: may be helpful to the reader to define the terms that some think are interchangeable but there are subtle differences GER: passage of gastric contents into the esophagus with or without regurgitation vomiting GERD: when GER leads to troublesome symptoms that affect daily functioning and/or complications Regurgitation: passage of refluxed contexts into the pharynx or mouth Vomiting: forceful expulsion of gastric contents through mouth.
Rosen, R., Vandenplas, Y., Singendonk, M., Cabana, M., Di Lorenzo, C., Gottrand, F., ... & Tabbers, M. (2018). Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). Journal of pediatric gastroenterology and nutrition, 66(3), 516.

Reply: Thank you so much for the article! We have exclusively decided to use GER in our review and shy away from using GERD as most were caregiver-reported/ undiagnosed by a

medical professional. We have included this article for another purpose from your later comment. We have included basic definitions of GER and GERD on page 12 lines 15-18.

Page 8 line 6 May be good to highlight how the authors are defining the terms, since I don't think pH impedance was used to determine if the material entered the pharynx (regurg), and vomiting was the authors sign of "reflux"

Reply: See page 8, line 13
Changes in the text: "signs associated with reflux in their infants at the start of the study (i.e., arching of the back, unable to lay flat after eating)."

Page 10 lines 10-12. The sentence "not included in this in ankyloglossia" doesn't flow well/make sense with previous sentence

Reply: We decided to clarify what we intended for this sentence. See page 11, line 2- 4
Changes in the text: "However, within review, there were both statistically and clinically significant improvements in reflux following treatment of ankyloglossia via frenotomy."

Page 10 lines 21 the aerophagia is an interesting and important outcome but it is previously written that it is dx by auscultation (assume stethoscope) and this sentence references paper where caregivers were noting aerophagia, assume not with stethoscope?

Reply: We decided to clarify what we intended for this sentence. See page 11, line 12-14
Changes in the text: "Aerophagia was also one of the caregiver-reported signs present in infants with ankyloglossia (10), though this cannot be confirmed without physical examination or radiographic studies."

Page 11 line 6: the case study did not present regurgitation (I think you're confusing that with significant pharyngeal residue) can you maybe say significant dysphagia resulting in need for enteral feeding tube (Which can promote reflux)? You could add here about the nasopharyngeal regurgitation which the case study showed- don't see another reference where NP regurgitation was associated with ankyloglossia but I may have missed, I do think it's related though!

Reply 1: See page 12, line 10-12
Changes in the text: "A case study by Brooks et al showed aspiration and significant dysphagia during feeding for one infant with ankyloglossia. This was postulated to cause reflux and needs to be evaluated in future research with a larger sample."

Page 11 line 12: definitely read this paper to see how this part needs to be edited as GIs are getting away from PPIs for reflux in infants
Rosen, R., Vandenplas, Y., Singendonk, M., Cabana, M., Di Lorenzo, C., Gottrand, F., ... & Tabbers, M. (2018). Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). Journal of pediatric gastroenterology and nutrition, 66(3), 516.

Reply: Thank you so much for the article. Upon review, we decided to add your reference into the review to suggest possible treatments for GERD. See page 12, line 9.
Changes in the text: “The recommended treatment for gastroesophageal reflux are thickened liquids, hydrolyzed protein-based formula, or invasive pharmacological treatment (27, 28).”

Reviewer B

While this could provide important and very useful content, I have several concerns that I hope the authors will be able to address. I am listing them in no particular order, below.

1. In my training, "signs" and "symptoms" were two different concepts. I had to check again, to be sure this was still in practice and I found several resources that explained that "signs" are objective and "symptoms" are only evident to the patient/person. However, it was also noted they are often used interchangeably. Despite that, I strongly recommend the authors review their document and consider each instance of the use of either word, and attempt to use the defined terms (except when reporting on how others use them, which may differ). I just think this will provide the most clarity to the most readers.

Reply: We have reviewed the definition of signs and symptoms using the reference below. Signs defined as the objective/observable evidence of the disease while symptoms are subjective/patient-reported evidence of the disease. We decided that it would be clear to use ‘signs’ throughout the review. From our previous reviewer, “by definition symptoms are reported, and clearly these infants do not "report" - others infer symptoms by signs”.
Reference:
Sign or symptom (concept ID: C3540840) - MedGen - NCBI [Internet]. U.S. National Library of Medicine; [cited 2023 Aug 7]. Available from: https://www.ncbi.nlm.nih.gov/medgen/761917
Changes in the text: signs/symptoms to signs

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2. In general, I perceived that though most of the components to a traditional scientific manuscript were present, they were not always in the place one would expect. This begins in the introduction, as there does not appear to be a clear rationale for how g.i. morbidities might be associated with ankyloglossia. For example, we do not see any discussion of WHY ankyloglossia might be related to reflux until the middle of page 8. It seems it should come much sooner. Another example is in section 4.1 (page 11), where I believe it is first suggested that reflux itself might also be overdiagnosed. It really seems like a discussion about the prevalence of (often self-diagnosed) reflux would be an important part of the background the authors are building on. In addition, there should be some discussion about how it largely resolves over a few months in this age group (reflux, not necessarily ankyloglossia). I just think the paper takes great leaps without providing a good base. This is an exceedingly complex area, and is understandably very difficult to organize succinctly. However, I think it is critical to address what is "normal" vs what is actually likely to be worthy of intervention.

Reply: We have edited and clarified our points in the manuscript from intro to conclusion. I hope you find that your review was well-utilized in our edits including addressing "normal". See page 11 line 9-11.

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3. In terms of article selection, were there any parameters placed on the time period searched? Could the authors provide that, if so.

Reply: A time parameter was not placed in the search due to the limited amount of research on this topic. We wanted to ensure that all relevant articles were accessed. See page 6, line 3-5
Changes in the text: "In addition, due to the limited published work regarding ankyloglossia, time parameter was not considered so as to increase access to all information regarding the topic."

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4. in the footnotes of tables 1 and 2, the authors state that having a p-value of

Reply: Unfortunately, the comment was cut-off, but I hope we were able to clarify the footnotes of each table.
Changes in the text: "**P-value is considered statistically significant $P \leq 0.05$; demonstrating that there is a relationship between the two variables in the study or that the relationship between reflux and ankyloglossia correction are not by chance. 31"

Overall, I would strongly recommend a critical look at the organization of the paper, bolstering the introduction to fully support the review of these concepts, and potentially invite a statistician to be coauthor, to reinforce appropriate interpretation of findings. I hope this feedback was helpful as I do believe this could help provide a pathway into interesting areas of future research and potentially practice.

Reply: We hope that you find the changes we have made in the overall text to have enhanced the readability and clarity of the review.

Reviewer C

Overall, I find the article to be a valuable contribution to the field, providing important insights into the gastrointestinal signs associated with ankyloglossia in infants and the impact of frenotomy as a surgical intervention. The research presented is relevant and addresses a gap in the current literature.

The study offers a comprehensive scoping review that examines seven relevant articles on gastrointestinal signs and symptoms in infants with ankyloglossia. Notably, the authors focus on the prevalence of gastroesophageal reflux in this population, a common symptom among infants below 6 months of age. The findings suggest that untreated ankyloglossia is associated with significant gastrointestinal reflux, as indicated by the mean I-GERQ-R total scores. This demonstrates the importance of addressing restricted tongue mobility in infants to alleviate reflux symptoms.

The article presents the impact of frenotomy as a surgical intervention for ankyloglossia, highlighting the improvements in tongue mobility and swallowing following the procedure. The mean I-GERQ-R total scores show a decrease at multiple postoperative time points (1 week, 1 month, and 6 months), indicating a positive effect on reflux symptoms. The statistical significance of the differences in scores before and after surgery further supports the efficacy of frenotomy in reducing gastrointestinal signs associated with ankyloglossia.

However, I would like to address a concern regarding the readability and clarity of the article. While the information presented is comprehensive, the text tends to be wordy and could benefit from refinement. Some sentences are overly long and may confuse readers, hindering the flow of information. I recommend the authors consider rephrasing certain sections to enhance readability and make the article more accessible to a broader audience. Simplifying complex concepts and using concise language would greatly improve the overall reading experience.

In summary, I believe the manuscript is well-structured and provides valuable insights into the gastrointestinal signs associated with ankyloglossia in infants. The findings on the effectiveness of frenotomy as a surgical intervention are particularly significant. I recommend that the article be accepted for publication, with the suggestion to refine the writing style to improve clarity and readability.

Reply: I hope that you find the changes we have made in the overall text to have enhanced the readability and clarity of the review.

Reviewer D

The introduction builds a logical case, and the research purpose is well constructed. The gaps in literature are somewhat discussed but may need to be explored further. Particularly the limitations and bias of the studies presented need to be more clearly stated. The methods of the study were well presented and appropriate for the question being asked. The review of the validity of the instruments used were strong and acknowledged the potential recall bias.

Recommendations:
- Address more clearly the controversy in literature. There are several studies and commentary that suggest that there is a lack of biologic plausibility or enough clear data

Reply: Thank you. We hope that you find the changes we have made in the overall text to clarify our goal within the review and that we have better highlighted the limitations of the research critiqued.

- Further explore and address the limitations and bias of the studies: namely definitional confusion, effects of the passage of time, lactation consultant support and the lack of control groups. Also consider the extensive research over the past three decades that has established that reflux in the first 6 months of life is benign, even though increased reflux frequency may correlate with unsettled infant behavior.

Reply: We hope to have clarified the limitations and bias of the studies within the edited review article e.g., see page 7, line 18 or page 10, lines 7-13. We have also added additional information regarding the benign nature of reflux in infants.

- The reference from 2001 on treatment of reflux in infants is outdated. The recommendation is now against treatment with acid reducing medications (for example Multicenter, double-blind, randomized, placebo-controlled trial assessing the efficacy and safety of proton pump inhibitor lansoprazole in infants with symptoms of gastroesophageal reflux disease PMID: 1905452). Update your information or remove this section.

Reply: Thank you for giving attention to this outdated recommendation. A reviewer suggested an article: Rosen, R., Vandenplas, Y., Singendonk, M., Cabana, M., Di Lorenzo, C., Gottrand, F., ... & Tabbers, M. (2018). Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). Journal of pediatric gastroenterology and nutrition, 66(3), 516.

Upon review, we decided to add your reference into the review to vaguely suggest possible treatments for GERD. See page 12, line 9.

Changes in the text: "The recommended treatment for gastroesophageal reflux are thickened liquids, hydrolyzed protein-based formula, or invasive pharmacological treatment (27, 28)." We also added more information about risk associated with medications, and other methods to reduce signs.

Second Round

Editorial Comments (Please do not delete this section. Editorial comments should also be replied point by point)

Many thanks to the authors for revising the manuscript based on the comments. However, there are still some issues that need to be addressed regarding the reporting following the PRISMA-ScR Checklist. Please see the comments below.

Reporting Checklist
1. We suggest authors fill out and submit the "PRISMA-ScR Checklist" (https://cdn.amegroups.cn/static/public/12s_PRISMA-ScR-Fillable-Checklist.pdf?v=1679367333471). The relevant page/line and section/paragraph number in the manuscript should be stated for each item in the checklist.
A statement "We present the following article in accordance with the PRISMA-ScR reporting checklist" should be included at the end of the "Introduction". The manuscript should also include a Reporting Checklist statement at the end of the text ("Footnote"): "The authors have completed the PRISMA-ScR reporting checklist."
Reply 1: We have added the footnote and statement at the end of introduction.
Changes in the text: See PRISMA-ScR reporting checklist; page 6 line 15-16; and see page 16 under section "Footnote"

Abstract
2. The abstract is too short and not informative enough (200-350 words max). Please add the background on gastrointestinal signs in infants with ankyloglossia to the "Abstract-Aim" to clarify the clinical significance and importance of this review. Also, please replace the subheading "Aim" with "Background".
Reply 1: Changed the wording from Aim to Background, included inclusion criteria in methods portion as well as additional information in the background. Previously around 180 words, now at 295 words.
Changes in the text: See Page 2, Abstract

3. The methodology of a scoping review is very important and also requires a brief description of the process in the Abstract. For the "Abstract-Methods" section, please also report the timeframe (e.g., "from inception until March 31, 2023"), and inclusion and exclusion criteria.
Reply 1: Added inclusion and exclusion criteria and timeframe for search
Changes in the text: See page 2, line 11-14

Highlight Box
4. Please also summarize "What is known and what is new?" in the highlight box.
Reply 1: Added section
Changes in the text: See Highlight box

Introduction

5. "In 2020, a panel of pediatric otolaryngologists published a definition of ankyloglossia in the Clinical Consensus Statement as “a condition of limited tongue mobility caused by a restrictive lingual frenulum” (2, p.473)". Please add the reference.
Reply 1: Reference included, see reference #4
Changes in the text: see page 17, line 10

Methods
6. Similar to the points of comment 3, please specify the timeframe. Simply stating "time parameter was not considered" may not be informative enough.
Reply 1: Clarified as to which the time parameter was with regards to the research articles and why not considered
Changes in the text: See page 7, line 9-10

7. Please specify the language consideration.
Reply 1: Included “written in the English language” as an inclusion criteria
Changes in the text: Page 7, line 6

8. For the selection process, please also specify how many reviewers screened each record and each report retrieved, and whether they worked independently.
Reply 1: All of the articles were screened by the first author however, all included articles were independently reviewed by both authors
Changes in the text: Page 7, line 16-23

9. For the data collection process, please also specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, and any processes for obtaining or confirming data from study investigators.
Reply 1: Processes have been specified and explained.
Changes in the text: Page 7, line 16-23

10. "After 12 duplicates were removed, a total of 115 articles were found". It should be 17 duplicates (12+5).
Reply 1: Corrected – per PRISMA diagram.
Changes in the text: See page 7, line 3-4

11. "A pre-set filter of infant per PubMed and CINAHL determined infancy age to range from 1 months to 23 months". It should be "from birth to 23 months" according to the filter.
Reply 1: Corrected
Changes in the text: See page 7, line 8

12. "Kleinmann" should be "Kleinman".
Reply 1: Corrected
Changes in the text: See page 8, line 16

Results

13. Table 1-footnote: "**P-value is considered statistically significant P ≤ 0.05". No "**" in table 1.
Reply 1: Added “**”
Changes in the text: See Table 1

14. "Hill et al (22) found approximately eight percent (n=37) of 113 mothers had a concerns about infantile reflux". Please re-check the data (113*8%=9 instead of 37).
Reply 1: Thank you. This has been corrected to state that approximately 12 percent (n=13) of 113 mothers had concerns about infantile reflux.
Changes in the text: See Page 10, line 3-4

15. "There was a significant decrease in I-GERQ-R scores at both one and six-month time points (Table 1). A statistically significant decline in total I-GERQ-R scores were present in all four studies (Figure 2)". However, only one p value was given for each study in Table 1. It is recommended that the authors add the p values for preoperative vs. 1 week postoperative or 1 month postoperative (there should be a total of 8).
Reply 1: Table 2 had the P-values for each study however, taking into consideration combining Table 2 and Figure 2 – we have noted in the text that all P-value are <0.05 with references to the original articles.
Changes in the text: See page 10, line 13-14

16. Table 2 and Figure 2 show the same results and it is recommended that they could be combined.
Reply 1: Combined; added footnote regarding other relevant results found in table 2 that was not originally found in figure 2. Corrected any reference for Table 2 to Figure 2.
Changes in the text: See Figure 2

17. Table 2: It is necessary to specify which two groups the p-values compare for statistical significance.
Reply 1: Combined with figure 2, same as comment #16
Changes in the text: See Figure 2

Discussion
18. We recommend including a separate section on the STRENGTHS and LIMITATIONS of this review to promote a more intellectual interpretation.
Reply 1: Added Strengths along with Key Findings and created a section for limitations.
Changes in the text: See page 14, section 4.2

Format
19. We recommend authors use a structured Introduction and Discussion to increase readability. For more specific details, please refer to the Structure template (https://cdn.amegroups.cn/static/public/2.2.2-Structure%20of%20Scoping%20Reviews-template-V2022.11.4.docx?v=1692864059260) and Guidelines for Authors (https://pm.amegroups.org/pages/view/guidelines-for-authors#content-2-2-2 Scoping Review).
Reply 1: Followed structure as suggested above i.e. Footnotes and further clarifications as requested above

Changes in the text: See overall texts