

Dear Lian-Seng Ma,

We want to thank you for taking into consideration our Opinion Review: "Very Early Onset Perinatal Constipation: Can It Be Cow's Milk Protein Allergy?" for publication to the World Journal of Gastroenterology. We appreciated the reviewers' careful review and their critiques. In response to reviewers' comments and suggestions, we have revised the manuscript. Major revisions made are shown in BOLD in the revised manuscript. Our detailed responses to the Reviewers' specific comments and queries are enclosed.

We look forward to learning that our manuscript has been accepted for publication.

Yours sincerely,

A handwritten signature in black ink, appearing to be 'S. Cheng', written in a cursive style.

Sam X Cheng, MD, MSc, PhD

Reviewer's Comments:

Reviewer #1

We thank the reviewer for taking the time to review our manuscript. We sincerely appreciate your comments.

“Include the methods you used to review the literature, besides the key words.”

Author's Response: For reviewing the literature, we initially wanted to identify the actual incidence of various etiologies of perinatal constipation or delayed passage of meconium. The data we came across was surprising to notice that what we as providers previously considered as common diagnoses in patients with delayed passage of meconium, was actually not that common compared to cow's milk protein allergy (CMPA). This manuscript, as an opinion review, was primarily written to increase awareness of the CMPA in the perinatal period, as evident by the case series we referred to in the manuscript, Mandala et. al. Moving further, with our understanding that CMPA had two primary mechanisms, we used current literature to further our discussion of the likely mechanism present with development of CMPA during the perinatal period. We hope this clarifies some of our methods for literature review.

Once again, we thank you for taking the time to review this manuscript and we sincerely appreciate the feedback.

Reviewer #2

We want to thank you for taking the time to review our Opinion Review: “Very Early Onset Perinatal Constipation: Can It Be Cow's Milk Protein Allergy?”. We sincerely appreciate your comments. We have addressed your questions within the manuscript.

“Newborns with CMPA can present with perinatal constipation, and CMPA is premised on the mother or newborn drinking milk. So how many mothers in the study population drank milk before giving birth?”

Author’s Response: All the mothers of patients with perinatal constipation consumed dairy products during pregnancy. This statement has now been added to the revised manuscript (see pages 9-10)

“Cow’s milk allergens can pass through the placenta and amniotic fluid to sensitize fetuses and cause allergy. How long does this sensitization process last?”

Author’s Response: The exact timeline of the sensitization process remains unclear. According to a previous study published in 2002, approximately 56% of infants with CPMA had become milk tolerant at 1 year, 77% at 2 years, 87% at 3 years, 92% at 5 and 10 years and 97% at 15 years of age. The study was performed in typical form of CMPA and whether this applies to atypical CMPA in the perinatal population requires further investigation. This has now been discussed in the revised manuscript (see pages 9-10)

“How long do the allergens remain effective?”

Author’s Response: We do not know exactly how long the allergens remain effective, however, given our patients’ symptoms resolved following the 2 week elimination period of the allergen, it suggests that this could approximate the timeline of allergen effectiveness. This has now been discussed in the revised manuscript (see pages 9-10).

“As shown in Figure 1, when the cow’s milk protein allergen from maternal diet passes into the fetus, how does it further cause distal colon spasm, and what are the associated mechanisms?”

Author’s Response: We greatly valued this question and have added an additional focus paragraph to address this. It has been addressed on pages 7-8 of the manuscript (in bold). Briefly, we discussed that currently, there is no exact mechanism, however, per our literature search, there is suggestion that the allergic response involves neuromodulation of the enteric nervous system, leading to increased anal pressure at rest and difficulties stooling.

We hope to have addressed your comments within our revisions. We once again thank you for your time.