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- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*

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Date: Apr 12, 2024
Description: Transfer Letter
To:
From: "The Green Journal" em@greenjournal.org - Obstetrics & Gynecology
Subject: Transfer Letter
Attachment(s):

Ref.:Prenatal Predictors of Survival, Pulmonary Hypertension, and ECMO in Isolated CDH Undergoing Expectant Management, A Systematic Review and Meta-analysis
Dr. Hiba J Mustafa

I am transferring the above article to you because I believe it is well-suited to your publication.

Please see the Decision letter included below for our editors' and reviewers' comments on the article.

Regards,

Obstetrics & Gynecology

Obstetrics & Gynecology Decision Letter:

To:
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-24-432
04/12/2024

RE: ONG-24-432 ("Prenatal Predictors of Survival, Pulmonary Hypertension, and ECMO in Isolated CDH Undergoing Expectant Management, A Systematic Review and Meta-analysis")

Dear Dr. Mustafa:

Your manuscript has been reviewed by the Editorial Board and expert reviewers. Based on the Reviewers' comments and the Editors' reading of your manuscript, we are not able to accept it for publication. Although we have declined your manuscript, we would like to offer you an opportunity to have this work considered for publication in O&G Open (www.open.greenjournal.org), a new open access journal within the American College of Obstetricians and Gynecologists' portfolio of journals.

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We appreciate the effort that goes into the preparation of a manuscript and the disappointment when it is not accepted. Thank you for submitting your work to Obstetrics & Gynecology, and we look forward to future contributions from you.

Sincerely,

The Editors of Obstetrics & Gynecology

- -

STATISTICAL EDITOR COMMENTS:

Tables 2, 3, 4: Many of the comparisons had only 2 studies. If there are only 2 studies, one cannot with any precision estimate the heterogeneity I^2. Should omit for those cases. Suggest emboldening or otherwise highlighting the odds ratios and MDs that were statistically significant, for easier readability.

Figures: Most figures have studies with subheadings "Left-sided", "Mixed" and their combination "Total". The "Mixed" contain all of same entries that are in the "Left-sided". That is, the "Left-sided" entries are actually a subset within the group labelled as "Mixed". Therefore, the entry for "Total" is statistically biased, since some studies are entered twice. If the left-sided are relevant to testing the association, then the others should be a distinct group, i.e., exclude the left-sided, then combine that non "Left-sided" for an aggregated estimate of "Total". Need to re-do these figures. Again, some of these figures had sections with only 2 studies, which is insufficient to reliably test for heterogeneity. The estimate of heterogeneity using I^2 statistic should be omitted in those cases.

REVIEWER COMMENTS:

Reviewer #1:

This is a systematic review of predictors of survival to discharge, persistent pulmonary HTN, and need for ECMO in congenital diaphragmatic hernia. The methods of review of studies are rigorous and well reported. However, the studies included and results reported are not "predictors" so much as "risk factors", given that they are primarily reporting associations and not ability of individual tests to predict outcomes. If predictive probabilities were reported, this would be more novel.

1. Abstract, line 30: define O/E with first use.

2. Introduction, lines 72-78: this is content that should be in results, not intro.

3. Introduction: In general, the intro reads as a listing of facts without drawing the necessary conclusions or motivation. Clearly explain why it is important to be able to predict outcome - would particularly high risk patients potentially benefit from FETO? Does better prognosis help families make decisions regarding pregnancy termination? It is already recommended that patients with fetuses with CDH deliver in centers capable of ECMO, so this would not change.

4. Methods, lines 124-125: did you require completion of negative genetic testing for inclusion?

5. Methods, lines 140-148: Please spell out acronyms the first time they are presented.

6. Methods, lines 158-159: double check this definition - it should be the percent of total liver volume that is herniated above the diaphragm.

7. Methods: Did you include studies that limited their population to higher or lower risk CDH? I ask because many of the fetal interventions trials were limited to high risk patients and thus this could skew your overall adverse outcome incidence.

8. Results: You do not cite the figures in your text. Please do so. Also, when you present the figures, are the ORs based on a cut-off value, or the measure treated continuously?

9. Results, lines 259-260: I understand that many of your liver based associations were not significant when only left-sided CDH was included. What is the n for these analyses? I wonder if this is because liver-up is less common with left-sided CDH. Are you powered to detect an association?

10. Discussion, throughout: You repeatedly refer to "predictors". In order for a test or a factor to be a predictor, you must know its predictive performance. None of this analysis has been presented here. You only have association statistics. I encourage you to rephrase this throughout.

11. Discussion, lines 291-292: Because there are previous similar analyses, you need to make it clear why this one was different/needed.

Reviewer #2:

This is a meticulously completed systematic review and meta-analysis that aims to identify prenatal predictors of survival, pulmonary hypertension, and ECMO in isolated CDH undergoing expectant management. I found this endeavor relevant with the goal to aid in prenatal counseling and coordination of care for fetuses with CDH. To strengthen this manuscript, the authors may wish to recognize best practices that have evolved in the measurement of the contralateral lung area on ultrasound, and its reproducibility (specifically the trace method). It may be interesting to look at the primary outcomes in the context of subgroups with congruent LHR and lung volume measurement methodology. It is important to know if the publications included in the meta-analysis have consist methods to obtain the various predictive measurements as the studies were pulled from at 23 year span.

It would be helpful to identify optimal gestational age for performance of prenatal lung measurements by ultrasound and MRI as they relate to primary outcomes and prediction of survival.

Reviewer #3:

This is a much needed review, since there is a pressing need to find objective predictors for PPHN and postnatal prognosis

There are a few queries:

1. The table shows two criteria- liver up and intrathoracic liver- while comparing the studies were they categorised differently? Both of them mean the same but may not be quantified by the same measurement.

The review spans over two decades, during which there have been considerable changes in detection and treatment, therapy has become more widespread and hence the studies too. Is this a contributor to the significant heterogeneity in certain studies?

Table 4 in prediction of ECMO after correction for left CDH the O/E LHR is significant but heterogeneity is 56%, how do we account for the influence of this on the results?
This study bears a lot of similarity to Ref 75 and draws a similar conclusion without much additional information. Additional parameters such as Liver intra thoracic ratio and percentage liver herniation by MRI may have been included which is a welcome addition since evolving new parameters may aid in development of better prognostic models for counselling mothers whose foetuses are diagnosed with CDH

Close

Date May 18, 2024

Re: “Prenatal Predictors of Survival, Pulmonary Hypertension, and ECMO in Isolated CDH Undergoing Expectant Management, A Systematic Review and Meta-analysis". ONG-24-432.

The Editors,

Obstetrics & Gynecology Open,

Dear respectful Editors,

Thank you for the opportunity to review our manuscript. We appreciate the conscientious review and constructive suggestions made by journal editors and reviewers. We believe that the manuscript is substantially improved after making the suggested edits.

Following this letter are the editor’s and reviewers’ comments with our detailed responses, including how and where the text was modified in the highlighted manuscript. The revision has been developed in consultation with all coauthors, and each author has approved the final form of this revision.

I appreciate your consideration.

Sincerely,

Hiba J. Mustafa, MD
Division of Maternal-Fetal Medicine
Department of Obstetrics and Gynecology
Indiana University, Riley Children’s Hospital
hmustafa@iu.edu

Response to Reviewers

REVIEWER 1

POINT 1:
Reviewer's comment: Abstract, line 30: define O/E with first use.

A. Authors' response : Thank you for your comment. The authors agree. Definition added
B. Lines 31-32
C. Text: "observed over expected (o/e)"

POINT 2
Reviewer's comment: Introduction, lines 72-78: This is content that should be in results, not intro.

A. Authors' response : Thank you for your comment. The authors agree. The paragraph was removed from the introduction.

POINT 3
Reviewer's comment: Introduction: In general, the intro reads as a listing of facts without drawing the necessary conclusions or motivation. Clearly explain why it is important to be able to predict outcome - would particularly high risk patients potentially benefit from FETO? Does better prognosis help families make decisions regarding pregnancy termination? It is already recommended that patients with fetuses with CDH deliver in centers capable of ECMO, so this would not change.

A. Authors' response : Thank you for your comment. The authors agree and have made the following changes as listed below.
B. Lines 68-71, and 75-78
C. Text: "Given the risks of mortality, persistent PHTN, and need for ECMO, different research groups have searched for antenatal predictors to personalize the prognosis of fetuses with severe CDH to allow improved prognostication for expecting parents, and appropriately prepare for neonatal resuscitation after birth. [11–21]"
"Accurate prognostication of disease severity in CDH (i.e. pulmonary hypoplasia or persistent PHTN) would also aid in appropriate patient triage, resource mobilization, and preparing for advanced postnatal treatment options such as ECMO for high-risk CDH, or those who may benefit most from fetal intervention procedures such as FETO."

POINT 4:
Reviewer's comment: Methods, lines 124-125: did you require completion of negative genetic testing for inclusion?

A. Authors' response: Thank you for your comment. The authors included isolated CDH defined as having no association with other structural and genetic anomalies and that is outlined in the methods section lines 115-116.

POINT 5:

Reviewer's comment: Methods, lines 140-148: Please spell out acronyms the first time they are presented.

A. Authors' response: Thank you for your comment. The authors agree. Acronyms were spelled out.
B. Lines 131-140

POINT 6:

Reviewer's comment: Methods, lines 158-159: double-check this definition - it should be the percent of total liver volume that is herniated above the diaphragm.

Authors' response: Thank you for your comment. The authors double-checked. *Percentage liver herniation (%HL)* was defined as the ratio of the volume of herniated liver volume to total fetal liver volume.

POINT 7:

Reviewer's comment: Methods: Did you include studies that limited their population to higher or lower risk CDH? I ask because many of the fetal intervention trials were limited to high risk patients and thus this could skew your overall adverse outcome incidence.

A. Authors' response: Thank you for your comment. The authors excluded cases that underwent fetal intervention (FETO) as mentioned in the methods, lines 116-117. The authors agree with the reviewer in that these pregnancies can skew results, hence they were excluded.

POINT 8:

Reviewer's comment: Results: You do not cite the figures in your text. Please do so. Also, when you present the figures, are the ORs based on a cut-off value, or the measure treated continuously?

A. Authors' response: Thank you for your comment. Figure 1 is cited as seen in line 188. Forest plots were cited as supplementary 2, 3, and 4 in lines 230, 237, and 252, respectively. Regarding OR and MD. Our methods in lines 174-176 state the following
   "Pooled effect sizes were presented using mean difference (MD) or odds ratio (OR), using the Mantel-Haenszel test, with 95% confidence interval (CI) for continuous and categorical variables, respectively".

POINT 9:

Reviewer's comment: Results, lines 259-260: I understand that many of your liver based associations were not significant when only left-sided CDH was included. What is the n for these analyses? I wonder if this is because liver-up is less common with left-sided CDH. Are you powered to detect an association?

Authors' response: Thank you for your comment. The authors agree. It certainly could be possible that the degree of severity of liver herniation is lower in left-sided CDH, which could

make these associations not significant. The n for left-sided CDH, with liver up, was 8 studies with a total n of 492 as shown in Table 2.

POINT 10:
Reviewer's comment: Discussion, throughout: You repeatedly refer to "predictors". In order for a test or a factor to be a predictor, you must know its predictive performance. None of this analysis has been presented here. You only have association statistics. I encourage you to rephrase this throughout.

A. Authors' response: Thank you for your suggestion. The authors agree. Predictors were changed to associations or index tests throughout as seen in lines 7, 14, 48, 73, and 266.

POINT 11:
Reviewer's comment: Discussion, lines 291-292: Because there are previous similar analyses, you need to make it clear why this one was different/needed.

A. Authors' response: Thank you for your suggestion. The authors agree. The authors report that the following additions were made.
B. Lines: 284-287, 289-290, 291, 294-295
C. Text:
   "They did not identify a clear predictor for PHTN, with analysis limited by the single-institution origin of many of the predictors available for meta-analysis, whereas our study did specifically assess predictors of PHTN and include many wide-ranging institutions."
   "Whereas we excluded all FETO-only studies"
   "whereas we performed a left-sided subgroup analysis for all categories."
   "Our study expanded on this to sub-analyze by laterality of herniation as well as a broader range of predictors."

REVIEWER #2:
POINT 1:
Reviewer's comment:
This is a meticulously completed systematic review and meta-analysis that aims to identify prenatal predictors of survival, pulmonary hypertension, and ECMO in isolated CDH undergoing expectant management. I found this endeavor relevant with the goal to aid in prenatal counseling and coordination of care for fetuses with CDH. To strengthen this manuscript, the authors may wish to recognize best practices that have evolved in the measurement of the contralateral lung area on ultrasound, and its reproducibility (specifically the trace method). It may be interesting to look at the primary outcomes in the context of subgroups with congruent LHR and lung volume measurement methodology. It is important to know if the publications included in the meta-analysis have consistent methods to obtain the various predictive measurements as the studies were pulled from at 23-year span. It would be helpful to identify the optimal gestational age for the performance of prenatal lung measurements by ultrasound and MRI as they relate to primary outcomes and prediction of survival.

A. Authors' response : Thank you for your positive feedback, comments, and suggestions. We do recognize the latest advancements in care including diagnosis and management. There is certainly heterogeneity in these measurement techniques, across institutions and countries. Given our time range, as well, this is difficult to include given the more recent development in these best practices. There is an inherent limitation of our study which is

reproducibility and methodology for obtaining fetal imaging tests. We included this in our limitations section as noted below. Unfortunately, there were very few studies reporting on gestational age and none that documented this on a gestational age-stratified basis.

B. Lines: 316-318
C. Text: "Additionally, there are notable limitations in measurement methodology, reproducibility, and institution protocols for sonographic and MRI measurements of CDH lesions and fetal lung volumes."

REVIEWER #3

POINT 1:

Reviewer's comment:

The table shows two criteria- liver up and intrathoracic liver- while comparing the studies were they categorized differently? Both of them mean the same but may not be quantified by the same measurement.

A. Authors' response : Thank you for your observation and very valuable comment. The authors point out that some studies specifically used a binary "up" or "down" and other studies did quantify the total percentage of intrathoracic liver, which supports using these as two separate criteria for assessment.

POINT 2:

Reviewer's comment:

The review spans over two decades, during which there have been considerable changes in detection and treatment, therapy has become more widespread and hence the studies too. Is this a contributor to the significant heterogeneity in certain studies?

A. Authors' response : Thank you for your comment and suggestion. The authors agree and edited the limitations section as seen in the lines below.
B. Lines : 316-318
C. Text: "Additionally, there are notable limitations in measurement methodology, reproducibility, and institution protocols for sonographic and MRI measurements of CDH lesions and fetal lung volumes, which have changed substantially over the timeframe included in our review."

POINT 3:

Reviewer's comment: In table 4 in the prediction of ECMO after correction for left CDH the O/E LHR is significant but heterogeneity is 56%, how do we account for the influence of this on the results?

Authors' response : Thank you for your comment. In the results section line 257, the authors report on the sensitivity analysis and show that No change in results was noted with leave-one-out analysis, and no publication bias was noted both by observing the funnel plots and by Begg's correlation test.

POINT 4:

Reviewer's comment:

This study bears a lot of similarity to Ref 75 and draws a similar conclusion without much additional information. Additional parameters such as Liver intra thoracic ratio and percentage liver herniation by MRI may have been included which is a welcome addition since evolving new parameters may aid in the development of better prognostic models for counselling mothers whose fetuses are diagnosed with CDH

A. Authors' response : Thank you for your comment. The authors agree there are certain similarities between Russo et al. and our study. We offer the additional strengths of excluding cases that underwent fetal intervention (FETO), as well as sub-analysis for right and left-sided CDH to further delineate the strongest predictors for the need for ECMO. Additionally, our study assessed survival which was not assessed in Russo et al. study.