Peer Review File

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Reviewer A

This is a noteworthy review of the advances in prenatal and postnatal management of Congenital Diaphragmatic Hernia (CDH). The authors are to be commended for their thorough review of the existing data on various subtopics within the prenatal and postnatal management of CDH. Overall, the topics were well covered.

Comment 1: Sections on the use of biomarkers in CDH management and postnatal genetic testing may be beneficial to add.
Reply 1: Since the article focuses on integrating prenatal and postnatal care perspectives, we have focused on the prenatal genetic testing approaches. The references utilized also cover the postnatal testing if prenatal diagnostics have not been performed and accordingly cover this aspect. We feel that the biomarker use falls outside the scope of this article's focus and would prefer not to add a section on this specific topic.
Changes in the text: No changes have been made to the manuscript in response to this comment.

Comment 2: Introduction, Line 94, 95: " … resulting in more severe pulmonary hypoplasia at birth" The authors should provide a reference for this statement. Additionally, due to the recent attention given to the left-sided cardiac structures, It would be worth adding a line on the type of defect/ severity of the defect and its impact on postnatal cardiac function.
Reply 2: The references that support the statement on lines 94/95 are 11 and 12 (see page 4, line 95). The relationship between defect size and cardiac dysfunction is referenced by 101 (see Page 13, line 393).
Changes in the text: References 11 and 12 have been moved to the specific statement on defect size and pulmonary hypoplasia. The statement that the cardiac dysfunction may be proportional to the defect size has been added.

Comment 3: II. 2.3 Prenatal stratification of CDH severity, lines 165-173.
An additional pitfall with LHR that can be mentioned is LHR in a fetus with IUGR may be unreliable since the head circumference may be variable in reference to gestational age. A line on this may be added.
Reply 3: We recognize this additional limitation.
Changes in the text: A qualifying statement regarding the presence of fetal growth restriction was added (see page 6, lines 168-169).

Comment 4: III. 2.9 The multifactorial pulmonary hypertension of CDH, lines 384-388. iNO use in CDH is a complex topic, and the response to iNO is variable. It would be worthy to expand on how the use of pulmonary vasodilators can cause worsening cardiorespiratory status in the setting of LV dysfunction. A line on the results of the NINOS trial may be added. Additionally, there is newer literature on iNO use in CDH (Noh CY, Chock VY, Bhombal S, et al. Early nitric oxide is not associated with improved outcomes in congenital diaphragmatic hernia [published correction appears in Pediatr Res. 2023 Apr 12;:]. Pediatr Res. 2023;93(7):1899-1906. doi:10.1038/s41390-023-02491-8), which can also be mentioned.

Reply 4: We agree with the comment and have incorporated the suggested reference.
Changes in the text: Drug delivery is contingent on optimal ventilation, however, efficacy does not necessarily reduce the incidence of ECLS or mortality. Clinicians must also be wary of the adverse effects of pulmonary vasodilators, as efforts to increase pulmonary blood flow may overwhelm the underdeveloped left heart. Signs of such pathology include pulmonary edema exacerbated cardiac dysfunction (see page 13, lines 386-388).

Comment 5: Minor edit: Line 388 has a number 3 in superscript. Authors should provide relevant references for this line.
Reply 5: The superscript is replaced with reference 102 (see page 13, line 388).
Changes in the text: No changes have been made to the text.

Reviewer B

The authors have submitted a comprehensive manuscript reviewing the continuum of multidisciplinary care for fetuses/neonates with congenital diaphragmatic hernia, incorporating FETO. I have a several questions for the authors to assist in the interpretation of their manuscript.

Comment 1: The authors embrace the concept that the fetal lungs are "compressed" by the organ herniation. This may suggest that repair would allow the lung to expand with immediate benefit. Perhaps semantics, but this concept was the foundation for the emergent repair decades ago which has abandoned with an acceptance that normal lung growth is impaired/constrained, etc. If the authors agree, I would suggest, unless there are data to the contrary, that they adjust the "compressed" concept.
Reply 1: We agree to temper the language and have modified the introduction (see page 2, lines 58-60). Since the remainder of the manuscript discusses the risk stratification based on contralateral lung size, we feel that this concept is qualified sufficiently in the context of this discussion.
Changes in the text: Intrathoracic crowding and compression of the fetal lungs by abdominal organs predispose the neonate to intrinsic bilateral pulmonary hypoplasia and hypertension, which manifest after birth.

Comment 2: The utilization of maternal steroids in fetuses not anticipated to have a preterm delivery is still controversial and not embraced uniformly. Indeed, early CDHSG papers did not show benefit. I would encourage softening the use as an option that is being investigated, but not promoted as routine care.
Reply 2: We agree that the language should be softened and have modified the sentence (see page 10, lines 300-301).
Changes in the text: "a single course of maternal steroid administration can be considered in the week prior to delivery irrespective of gestational age."

Comment 3: Line 42: Consider substituting "utilize" for "require" ECMO as this is a supportive therapy that is offered as part of the armamentarium, not mandatory.
Reply 3: We agree with this suggestion and have made this modification in two places.
Changes in the text: "In about 25-30% of CDH neonates extracorporeal life support is utilized (see page 2, lines 41-42); "where ECLS was not utilized" (see page 16, line 480).

Comment 4: Line 56/57. See point #1. Would word that the fetus has intrinsic pulmonary hypoplasia (bilateral) which manifest at birth (along with the pHTN).
Reply 4: We agree with the suggested change.
Changes in the text: The sentence has been modified as indicated in response to comment 6 (see page 2, lines 58-60).

Comment 5: Line 109. Please check the 60% prenatal dx…is this for both R and L? The CDHSG would suggest ~74% in all comers.
Reply 5: We agree with the statement and have updated the percentage.
Changes in the text: "up to 74%" (see page 4, line 109).

Comment 6: Line 163-5. Please tell the reader the year LHR was published for a historical frame of reference. Consider same for FETO, line 241. Would consider a very brief overview of Dr. Harrison's pioneering work in open repair, open tracheal occlusion that led the way to FETO.
Reply 6: The years were added as suggested (see page 6, line 163 and page 8, line 240) and we added a brief comment referencing Dr. Harrison's work.
Changes in the text: At the same time prenatal CDH repair, or open surgical techniques for tracheal occlusion did not improve outcomes and were associated with significant infant morbidity and mortality (see page 8, line 240).

Comment 7: Line 183. Consider using "fetuses" in place of "patients"
Reply 7: We agree with this change.
Changes in the text: The word "patients" was changed to "fetuses" (see page 6, line 183).

Comment 8: Line 212. Loss of lung volume is confusing. See comment #1 above.
Reply 8: We modified the statement to reflect measurable lung dimensions (see page 8, line 212).
Changes in the text: Prenatally acquired pulmonary hypoplasia, which is proportional to the decrease in lung dimension

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Comment 9: Would tell the reader about FETO not being "standard of care" and discuss current status of the intervention as still under investigation, need for IND, trial status, etc.
Reply 9: We agree with adding a statement regarding the need for an IDE in the United States (see page 9, line 277). We prefer to maintain the discussion of the available level 1 evidence as it is currently presented in the manuscript.
Changes in the text: In the United States, FETO can currently only be offered under an investigational device exemption with the oversight of the Food and Drug Administration.

Comment 10: In section 2.7, consider addressing the level of oxygen used at birth for neonatal resuscitation as there is data in "normal" newborns to start at RA and escalate due to concern of free radicals vs. starting at 100% and weaning as able to mitigate pHTN. Is Gastric decompression appropriate to address to maximize lung excursion?
Reply 10: We agree with this comment and have added additional text and references.
Changes in the text: Oxygen should be offered judiciously, as excessive exposure may attenuate the subsequent efficacy of nitric oxide, should it become necessary later in the infant's care (see page 11, lines 309-310). Gastric decompression was added as key element at delivery (see page 11, line 325).

Comment 11: Lines 383-2382. Agree with IGNORING post-ductal as long as lactate OK. Consider role of lactate to assure adequate tissue perfusion.
Reply 11: We agree with this comment and have added lactate as a monitoring parameter (see page 13, lines 381-382).
Changes in the text: Saturations, PO_2, A-a gradients, and lactate levels used for judging progress and adequate tissue perfusion should all come from pre-ductal sources.

Comment 12: Line 498. Current CDHSG data would suggest a ~37% DC use of feeding tubes. Please clarify.
Reply 12: Thank you for your astute comment. Although institutional practices do vary with regards to nasogastric vs. gastrostomy tube feeds, we acknowledge that the use of feeding tubes is quite high (over 30%). We also concur that this is an under-recognized aspect of postoperative CDH care. We have revised the manuscript accordingly and have included a CDHSG reference from Putnam et al (see page 17, lines 495-507).
Changes in the text: More than 30% of infants are discharged on supplemental tube feeds, and over 10% received surgical feeding tube procedures (e.g., gastrostomy tubes) to ensure caloric needs owing to poor oral feeding.

Comment 13: Line 528. Please tell the reader how you define pHTN at DC; ECHO finidngs or need for treatment with oxygen or medication?
Reply 13: We recognize that there is a range of findings that may suggest persistence of pulmonary hypertension. We have qualified the clinical markers that point to chronic vascular disease in the lungs and added to new references.
Changes in the text: We have added the following sentence at line 400: “Though CDH is inherently associated with pulmonary hypertension related to vascular remodeling, only a subset will proceed to experience clinically significant chronic pulmonary vascular disease. Infants who require pulmonary vasodilator therapy during hospitalization, are discharged on pulmonary vasodilators, or have significant echo findings have been found more likely to have chronic disease.” New references 135 and 136 have been added.

Comment 14: Would add that nutritional morbidity is very significant as well.
Reply 14: We agree and added additional language to the Discussion.
Changes in the text: Nutritional status affects approximately 25% of survivors but tends to improve during the first year of life.