**The Editor, Journal of Pediatric Surgery**

**RE: Fetal Surgery For Moderate And Severe CDH – The TOTAL Trials (1,2)**

**September 5th 2021**

Editor:

As Pediatric Surgeons who have long struggled with the care of neonates with severe Congenital Diaphragmatic Hernia (CDH), we read with great interest the long awaited results of the TOTAL trials on the application of Fetal Endoscopic Tracheal Occlusion (FETO) to fetuses effected by moderate and severe CDH**(1,2).** We first congratulate Professors Deprest, Nicolaides, and colleagues for their dogged persistence on completing these very challenging trials. We must, however, emphasize that the results of these trials represent only a promising beginning of the investigative work that needs to be done to define the role of FETO in the treatment of fetuses with CDH. FETO should *not* be interpreted as a green light for broad application of this potential therapy.

While every effort was made to design these trials to minimize variables between treatment groups, there are limitations in what was possible given the multicenter design. The ability to standardize care during an 11 year trial across 10 FETO centers and 26 (severe)/36(moderate) neonatal centers of widely varied experience in the care of CDH and the use of ECMO, must be questioned. Because standardized protocols existed**(3)** did not mean that they were executed equivalently. Moreover, it is well documented that the results of neonatal CDH care are highly dependent on the experience of the neonatal center. These concerns are validated by the very low survival in the severe trial control group (only 15%), and the reported diaphragmatic repair rates of only 53% in the severe FETO group and 36% in the severe control group. This raises concern for investigator bias toward repair of FETO patients (the study could not be blinded) and for the criteria used for repair. Similarly, only 5% of FETO patients and 29% of control patients in the severe trial were placed on ECMO. These are exceedingly low ECMO rates for groups that ultimately had a 60% and 85% mortality rate respectively, suggesting that ECMO was not adequately utilized to optimize survival.

This is important when considering the translation of these results to other environments such as North America where major advances in post-natal care involving respiratory care strategies based on permissive hypercapnia/spontaneous ventilation and extracorporeal life support have generated significantly improved outcomes in prenatally stratified, severe CDH patients**(4,5).** It should be pointed out that previous trials of fetal repair or FETO for severe CDH have failed to show benefit because of unexpectedly good outcomes in the control groups where post-natal care in the center had improved in the interim**(6).** What would the results of this trial have been in centers where survivals of severe CDH patients are now reported to be above 60%?

Because only 12% of potential fetuses were entered into the severe group, exclusion based on “chromosomal abnormalities” should be detailed, as most genetic information regarding CDH derives from detailed genomic sequencing of post-natal tissue or physical exam**(7).**

It is also important to note that the TOTAL trials were not powered adequately for morbidity outcomes and demonstrated no improvement in morbidities in either population. The goal of treatment of CDH, particularly in environments that have optimized survival of these infants, must be reduction in the chronic, quality of life impacting morbidities suffered by survivors of this condition. A therapy that improves survival in CDH without corresponding improvement in morbidities must be carefully evaluated for its overall benefit. Given the devastating impact that prematurity is known to have on survival and morbidity of severe CDH patients, and the rates of prematurity inherent to FETO (65% of FETO patients in the severe trial were born prior to 34 weeks gestation) it is hard to imagine that there is not a detrimental effect of prematurity associated with this therapy. Future trials must be adequately powered to assess morbidity outcomes and the effects of prematurity.

In summary, the results of the TOTAL trials should stimulate additional studies to clarify the results of this intervention. They should not change the current counselling or treatment for most fetuses diagnosed with CDH, and should not be used as a justification for treatment by FETO outside of well designed trials by experienced high volume fetal centers. FETO should not be represented to vulnerable prospective parents as standard of care or anything other than investigational. Finally, the impact of FETO should not be considered independently from the impact of improved neonatal care.

Charles J.H. Stolar, MD, Columbia University, Vagelos College of Physicians and Surgeons

Jay M. Wilson, MD, Harvard University, School of Medicine

Paul D. Losty, MD, Faculty of Health and Life Sciences, University of Liverpool, UK

Alan W. Flake, MD, University of Pennsylvania, Perelman School of Medicine

References

1. NEJM 2021;385:107-118
2. NEJM 2021;385:119-129
3. Neonatology 2016;110:66-74
4. J Pediatr Surg 1995;30(3):406-409
5. J Pediatr Surg 1997;32:401-405
6. NEJM 2003;349:1916-1924
7. Hum Mol Genetics 2015;15(8):4674-4673