Congenital Diaphragmatic Hernia: An Update on Management Strategies and Outcomes

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Abstract

Congenital diaphragmatic hernia (CDH) is a severe developmental anomaly associated with high mortality and long-term morbidity. Right-sided defects (RCDH) are less common than left-sided (LCDH) with variable outcomes and survival rates reported in the literature that are more frequently worse than for infants with left hernias.

RCDH has been associated with increased severity of pulmonary hypoplasia and increased incidence of pulmonary hypertension. Long-term respiratory, surgical and musculoskeletal morbidity also appears greater in infants with RCDH that tend to have a higher proportion of larger defects. Laterality alone is not an independent predictor of survival but gestational age, being small for gestation, the size of the defect and antenatal assessment of the fetal lung size have been identified as independent predictors of survival. Fetoscopic endoluminal tracheal occlusion (FETO) in the antenatal period improves survival rates in infants with severe left or right CDH and seem to improve the morbidity associated with right-sided defects but it remains an invasive procedure with potential complications. Ongoing studies aim to reduce FETO-associated complications and to develop adjunct therapies, such as stem cells or sildenafil, that could promote fetal lung growth and maturation and target pulmonary hypertension.

As mortality and morbidity of CDH survivors remain high and till results from the above studies become available, following a structured antenatal and postnatal management of CDH patients with standardised follow up of survivors could help improve neonatal outcomes.

Congenital diaphragmatic hernia (CDH) is a severe developmental anomaly with an estimated global prevalence at birth of about 2.3 in 10,000 live births [1]. Despite recent advances in antenatal diagnosis, fetal interventions and postnatal management, the condition continues to have a high mortality due to pulmonary hypoplasia and pulmonary hypertension [2,3] and affected infants can suffer long-term morbidity. In a prospective national population cohort study from the United Kingdom and Ireland, the overall survival to one year of infants with CDH was 75% with the majority of deaths occurring before surgical repair [2]. Right-sided CDH (RCDH) is less common than left-sided defects and accounts for 15-20% of all CDH cases and there is conflicting evidence as to whether it represents a more severe condition with different outcomes [4-6]. Reported survival rates for infants with RCDH have been variable, but more frequently are lower than for infants with a LCDH [7,8]. In this commentary, we provide an updated summary of the literature on the outcomes of CDH infants with reference to the side of the defect and will present some ongoing studies of novel therapeutic management strategies.

We have previously reported that the morbidity and

mortality of infants with a right versus a left-sided CDH and highlighted whether any differences occurred in those infants who had undergone fetoscopic endoluminal tracheal occlusion (FETO) in the antenatal period [9]. Survival to discharge of the infants overall and in the FETO group did not differ significantly according to the side of the defect. Infants with RCDH, however, had a significantly higher need for inhaled nitric oxide (iNO) in the neonatal period and greater long-term respiratory, surgical and musculoskeletal morbidity at follow up. This included chronic cough or more than two respiratory admissions, hernia recurrence, pectus deformity and scoliosis. We did not, however, observe any significant differences in short or long-term morbidity following FETO according to the side of the lesion and speculate that the procedure may reduce the greater disadvantageous effects that occur in utero due to a right compared to a left sided hernia [9].

Previous studies comparing outcomes of right versus left CDH have also reported a higher risk of hernia recurrence [10,11] and need for patch repair in patients with RCDH [4,10], but no significant differences in survival. In a large multi-centre, international study which included 3754 cases of CDH, right-sided hernias had a higher proportion of larger defects [4]. Multivariable logistic regression analysis revealed a significant correlation between the size of the defect and survival, but not for laterality; similar survival rates were observed for similar defect sizes independent of the side of the hernia [4]. Larger diaphragmatic defects have also been associated with increased incidence of spinal and chest wall deformities [12] and in our series more RCDH infants who tended to have larger defects developed musculoskeletal abnormalities at follow-up, which was at least for one year and all those born in 2014 had at least four years follow-up [9].

We demonstrated an increased need for iNO in infants with RCDH. Previous studies had also highlighted an association between RCDH and increased pulmonary morbidities as evidenced by the higher requirement for treatment with pulmonary vasodilators and extracorporeal membrane oxygenation (ECMO) [4], prolonged oxygen treatment and increased requirement for tracheostomy [6]. Although mortality was not higher in RCDH infants in all those studies, the results may indicate an increased severity of pulmonary hypoplasia with an increased incidence of pulmonary hypertension in infants with RCDH.

More recently, a retrospective multicentre analysis comparing outcomes of right and left CDH infants suggested that laterality alone is not an independent predictor of morbidity and mortality [13]. In a cohort of 588 neonatal patients, infants with RCDH (n=93) were more frequently diagnosed with co-existing congenital heart defects (RCDH 29% versus LCDH 20%, p=0.046), but no significant differences were observed regarding other coexisting congenital anomalies overall or clinically evaluated genetic syndromes. RCDH patients were more likely to require a patch or muscle flap for repair with a thoracic approach likely due to the relatively larger size of the defect in agreement with previous studies [4,10]. There were, however, no significant differences in pulmonary or surgical complications including pulmonary hypertension, need for ECMO and hernia recurrence. At two-year follow up, neurodevelopmental outcomes were similar between the groups and within one standard deviation of the general population [13]. An eight-year review of 189 CDH pregnancies from a single institution revealed an increased association of right-sided defects with known antenatal predictors of poor perinatal outcomes (ultrasound evidence of liver herniation, ascites, pleural effusion or hydrops and a lower lung to head ratio (LHR)). Despite that association, infant survival to hospital discharge was similar with regards to laterality (64 versus 66.4%, p=0.49) with comparable obstetric (stillbirth, mode of delivery) and short-term neonatal (small for gestational age at birth, need for ECMO and length of stay at the Neonatal Intensive Care Unit) outcomes [14]. The study though did not report on long term morbidity and the authors emphasised that due to missing data they may have been underpowered in the analysis of adverse neonatal outcomes [14]. In agreement with the above, in a retrospective cohort study using the French national database of the Reference Centre for CDH, antenatal presence of liver herniation on ultrasound and a lower observed to expected lung-to-head ratio (o/e LHR) were independent predictors of mortality in a logistic regression model. Survival was higher for infants with LCDH compared to RCDH (77% versus 57%, p<0.01), but laterality was not an independent predictor after adjusting for liver herniation and O/E LHR. Infants with RCDH required significantly more frequently silo insertion, liver reduction and patch repair at surgery. Neonatal morbidity, pulmonary hypertension at forty-eight hours after birth, need for ECMO, oxygen therapy at twenty-eight days and the length of intensive care stay, were comparable between the groups [15]. Infants with CDH who had undergone FETO were excluded from the study and it was limited by a high rate of missing data for some variables. In a national population-based study in the UK and Ireland, survival of CDH patients to one year was also not related to the side of the diaphragmatic defect, but being small for gestation was identified as a risk factor for increased infant mortality and diaphragmatic closure with a patch was linked to an increased incidence of chylothorax and mortality due to the well-known association of large defects with adverse clinical outcomes [2].

A retrospective review of patients across four European FETO centres with standardised prenatal and postnatal

management strategies [16] included 214 cases with an isolated RCDH and demonstrated, that in expectantly managed infants, a larger fetal lung size assessed by either the observed to expected lung to head ratio on ultrasound or by the total fetal lung volume (TFLV) on MRI or a lower liver-to-thorax ratio (LiTR) on MRI were significantly associated with higher rates of survival at discharge from intensive care and length of hospital stay. It should be noted that the best cut-off value of the O/E LHR to predict survival was 50% with higher specificity than the previously used value of 45% [17]. TFLV on MRI had similar predictive ability with the O/E LHR. In the FETO group, gestational age was the only predictor of survival (OR (95% CI): 1.25 (1.04-1.5), p=0.02). Infants with severe pulmonary hypoplasia that had undergone FETO were more likely to survive to discharge (41% versus 15%, p=0.014) and the improvement in survival was sustained at six and twelve months of age. FETO cases had a higher risk of preterm prelabour rupture of membranes (PPROM) and preterm delivery when compared with cases of similar severity in the expectant management group. Despite earlier birth, neonatal morbidity indicators and the duration of intensive care stay did not differ significantly between the two groups. The authors concluded that FETO incurs a survival benefit to infants with severe isolated RCDH that outweighs the risk of prematurity related to the procedure. Mortality rates though remained high and comparable to these reported in earlier FETO studies [18] indicating that RCDH may constitute a separate entity with different biology and outcomes [6,18,19].

The outcomes of the infants with an isolated LCDH post FETO were determined in two large multi-centre randomised controlled trials (Tracheal Occlusion to Accelerate Lung Growth trials for moderate or severe hypoplasia) which took place across twelve European FETO centres. Infants with severe isolated LCDH (O/E LHR of less than twenty-five per cent) randomised to FETO had increased survival rates at discharge when compared to the expectant management group (40% versus 15%, p=0.009) and the increase in survival was sustained until six months of age. As observed in infants with RCDH that had undergone FETO, the risks of PPROM and preterm delivery were higher, but there was no increase in the duration of ventilatory support, intensive care stay or other complications related to prematurity. It should be noted, however, the trial was not powered for those outcomes or for the less common maternal or fetal complications [20]. In moderate congenital diaphragmatic hernia on the left side (O/E LHR 25 to 34.9% irrespective of liver position, or 35 to 44.9% with intrathoracic liver herniation) survival of infants to discharge or survival without oxygen supplementation at six months was not greater following prenatal FETO when compared with expectant management. In that trial, the procedure was

performed at a later gestation (thirty to thirty-two weeks weeks) to account for the risk of preterm delivery and the authors speculate that this delayed occlusion of shorter duration could have contributed to the lack of significant improvement in survival [21]. Both trials required a long time period to complete during which protocols for postnatal management may have changed. The centres involved had high antenatal detection rates for CDH and experience in performing FETO. Therefore, the findings may not be generalisable to centres with different case mix or less experience in performing the procedure.

Although FETO seems to be of benefit in infants with severe CDH, it remains an invasive procedure with potential complications. Tracheomalacia and tracheomegaly have been reported [20-24]. In a retrospective, cross-sectional study of 37 CDH infants treated by FETO, tracheal diameter at birth measured on chest radiographs, was significantly increased in its whole length when compared with term and preterm controls, who were non-CDH neonates, matched for gestational age admitted at the Neonatal Intensive Care Unit with various pathologies including prematurity, respiratory distress and non-pulmonary problems [24]. Regression analysis showed that the severity of the CDH as measured by the pre-FETO O/E LHR and the duration of tracheal occlusion were significant predictors of the tracheal diameter at the level of tracheal entry into the chest. At follow up at the age of 22 months, about 20% of CDH survivors had an effort-induced barking cough. Early tracheal occlusion, especially before 26 weeks of gestational age, when the airways are highly compliant, also seemed to predispose to tracheomegaly [24,25]. With the exception of a few cases reported in the literature [23], tracheal issues appear to become less pronounced with age and clinical symptoms are very rare [22]. Cases of unsuccessful balloon removal prenatally or failure of postnatal puncture of the balloon leading to neonatal demise have also occurred [20,26]. In a cohort of 210 CDH cases that underwent FETO, ten deaths were reported as being directly related to difficulties with removal of the balloon and that was more likely to occur when the procedure was performed as an emergency. For those reasons, patients participating in the TOTAL trials were advised to stay near a FETO centre during the occlusion period. In the trials, two neonatal deaths were attributed to unsuccessful balloon removal that was also attempted postnatally [20,21]. Studies are under way to assess potential strategies to reduce FETO-associated complications [27-29]. Long-term outcomes of participants remain to be assessed.

Despite the advances in antenatal and postnatal management strategies, mortality due to pulmonary hypoplasia in infants with CDH remains high. In addition, survivors suffer from complex medical and surgical

problems that continue through childhood, adolescence and adulthood [30,31]. New treatments are being investigated that could facilitate fetal lung growth and maturation and target pulmonary hypertension in CDH infants including cell therapies and sildenafil. Mesenchymal stem cells are considered to play an important role in lung development and have a potential beneficial effect in the prevention or treatment of bronchopulmonary dysplasia in neonates [32]. Adjunct therapies using stem cells have been studied in animal CDH models. In a rabbit CDH model, tracheal occlusion combined with intra-tracheal injection of human amniotic fluid stem cells led to an increase in the number of alveoli and a trend towards a decrease in peripheral muscularization with no signs of toxicity [33]. In a more recent study of a nitrofen-induced rodent CDH model, intra-amniotic injection of human mesenchymal stem cells (hMSCs) into the CDH fetuses resulted in more alveoli, larger air spaces and thinner alveolar walls compared to that in the controls. The medial and adventitial thickness of the pulmonary arteries were also improved in the CDH-hMSCs group. These studies [32,33] show that stem cells may have a role in improving fetal pulmonary morphological abnormalities related to CDH and reducing pulmonary hypertension.

Inhaled nitric oxide (iNO), a pulmonary bronchodilator and vasodilator, is often the drug of first choice for pulmonary hypertension in CDH newborns. In term or near-term infants with persistent pulmonary hypertension of the newborn (PPHN) or severe hypoxic respiratory failure, iNO improves oxygenation and reduces the need for ECMO [34,35]. In CDH infants, however, mortality was not reduced and more ECMO treatment was needed [36,37]. Sildenafil improves oxygenation and reduces mortality in neonates with PPHN [38], but prospective data in CDH patients are lacking. A prospective, multicentre, international randomised-controlled trial (RCT) of iNO versus sildenafil for the treatment of pulmonary hypertension in neonates with CDH is under way. The trial will also report on long-term follow up at twelve months [39]. Antenatal sildenafil therapy has been studied in animal models and was shown to cross the placenta and improve pulmonary vascular resistance and airway morphometry [40]. A prospective randomised phase I/IIb trial evaluating the transplacental transfer of sildenafil in humans is ongoing [41].

In conclusion, the mortality of CDH remains high despite recent advances in antenatal interventions and postnatal management strategies. Laterality alone may not affect mortality, but there is some evidence to suggest that RCDH infants have greater morbidity compared to infants with LCDH due to the relatively larger size of the defect. FETO plays a role in the management of infants with severe left or right CDH improving overall mortality regardless of the side of the defect. Long-term follow up

data of participants in trials are necessary to review the impact of the intervention on long-term morbidity and to inform antenatal counselling and follow up planning of these patients. Future treatments may incorporate adjunct medical interventions such as stem cells or sildenafil to further optimize neonatal outcomes. A structured antenatal and postnatal management of infants with CDH based on the best available evidence along with standardised follow up of survivors is necessary if the morbidity and mortality of the disease are to improve.

Declaration of Interest

The authors have no conflict of interest.

Author Contribution Statement

All listed authors contributed equally to the manuscript.

References

1. Paoletti M, Raffler G, Gaffi MS, Antounians L, Lauriti G, Zani A. Prevalence and risk factors for congenital diaphragmatic hernia: A global view. Journal of Pediatric Surgery. 2020 Nov 1;55(11):2297-307.

2. Long AM, Bunch KJ, Knight M, Kurinczuk JJ, Losty PD. One-year outcomes of infants born with congenital diaphragmatic hernia: a national population cohort study. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2019 Nov 1;104(6):F643-7.

3. Wang Y, Honeyford K, Aylin P, Bottle A, Giuliani S. One-year outcomes for congenital diaphragmatic hernia. BJS Open. 2019 Jun;3(3):305-13.

4. Burgos CM, Frenckner B, Luco M, Harting MT, Lally PA, Lally KP, Congenital Diaphragmatic Hernia Study Group. Right versus left congenital diaphragmatic hernia–What's the difference?. Journal of Pediatric Surgery. 2018 Jan 1;53(1):113-7.

5. Duess JW, Zani-Ruttenstock EM, Garriboli M, Puri P, Pierro A, Hoellwarth ME. Outcome of right-sided diaphragmatic hernia repair: a multicentre study. Pediatric Surgery International. 2015 May 1;31(5):465-71.

6. Partridge EA, Peranteau WH, Herkert L, Rendon N, Smith H, Rintoul NE, et al. Right-versus left-sided congenital diaphragmatic hernia: a comparative outcomes analysis. Journal of Pediatric Surgery. 2016 Jun 1;51(6):900-2.

7. DeKoninck P, Gomez O, Sandaite I, Richter J, Nawapun K, Eerdekens A, et al. Right-sided congenital diaphragmatic hernia in a decade of fetal surgery. BJOG: An International Journal of Obstetrics & Gynaecology.

2015 Jun;122(7):940-6.

8. Brandt JB, Werther T, Groth E, Küng E, Golej J, Berger A. Risk factors for mortality in infants with congenital diaphragmatic hernia: a single center experience. Wiener Klinische Wochenschrift. 2021 Mar 30:1-6.

9. Ali K, Dassios T, Khaliq SA, Williams EE, Tamura K, Davenport M, et al. Outcomes of infants with congenital diaphragmatic hernia by side of defect in the FETO era. Pediatric Surgery International. 2019 Jul;35(7):743-7.

10. Beaumier CK, Beres AL, Puligandla PS, Skarsgard ED, Network TC. Clinical characteristics and outcomes of patients with right congenital diaphragmatic hernia: a population-based study. Journal of Pediatric Surgery. 2015 May 1;50(5):731-3.

11. Hajer GF, vd Staak FH, de Haan AF, Festen C. Recurrent congenital diaphragmatic hernia; which factors are involved?. European Journal of Pediatric Surgery. 1998 Dec;8(06):329-33.

12. Russell KW, Barnhart DC, Rollins MD, Hedlund G, Scaife ER. Musculoskeletal deformities following repair of large congenital diaphragmatic hernias. Journal of Pediatric Surgery. 2014 Jun 1;49(6):886-9.

13. Abramov A, Fan W, Hernan R, Zenilman AL, Wynn J, Aspelund G, et al. Comparative outcomes of right versus left congenital diaphragmatic hernia: A multicenter analysis. Journal of Pediatric Surgery. 2020 Jan 1;55(1):33-8.

14. Sperling JD, Sparks TN, Berger VK, Farrell JA, Gosnell K, Keller RL, et al. Prenatal diagnosis of congenital diaphragmatic hernia: does laterality predict perinatal outcomes?. American Journal of Perinatology. 2018 Aug;35(10):919-24.

15. Pinton A, Boubnova J, Becmeur F, Kuhn P, Senat MV, Stirnemann J, et al. Is laterality of congenital diaphragmatic hernia a reliable prognostic factor? French national cohort study. Prenatal Diagnosis. 2020 Jul;40(8):949-57.

16. Russo FM, Cordier AG, Basurto D, Salazar L, Litwinska E, Gomez O, et al. Fetal endoscopic tracheal occlusion reverses the natural history of right-sided congenital diaphragmatic hernia: European multicenter experience. Ultrasound in Obstetrics & Gynecology. 2021 Mar;57(3):378-85.

17. Jani J, Nicolaides KH, Keller RL, Benachi A, Peralta CF, Favre R, et al. Observed to expected lung area to head circumference ratio in the prediction of survival in fetuses with isolated diaphragmatic hernia. Ultrasound in Obstetrics & Gynecology. 2007 Jul;30(1):67-71.

18. Doné E, Gucciardo L, Van Mieghem T, Jani J, Cannie M, Van Schoubroeck D, et al. Prenatal diagnosis, prediction of outcome and in utero therapy of isolated congenital diaphragmatic hernia. Prenatal Diagnosis: Published in Affiliation with the International Society for Prenatal Diagnosis. 2008 Jul;28(7):581-91.

19. Fisher JC, Jefferson RA, Arkovitz MS, Stolar CJ. Redefining outcomes in right congenital diaphragmatic hernia. Journal of Pediatric Surgery. 2008 Feb 1;43(2):373-9.

20. Deprest JA, Benachi A, Gratacos E, Nicolaides KH, Berg C, Persico N, et al. Randomized Trial of Fetal Surgery for Severe Left Diaphragmatic Hernia. New England Journal of Medicine. 2021 Jun 8.

21. Deprest JA, Benachi A, Gratacos E, Nicolaides KH, Berg C, Persico N, et al. Randomized Trial of Fetal Surgery for Moderate Left Diaphragmatic Hernia. New England Journal of Medicine. 2021 Jun 8.

22. Deprest J, Breysem L, Gratacos E, Nicolaides K, Claus F, Debeer A, et al. Tracheal side effects following fetal endoscopic tracheal occlusion for severe congenital diaphragmatic hernia. Pediatric Radiology. 2010 May;40(5):670-3.

23. McHugh K, Afaq A, Broderick N, Gabra HO, Roebuck DJ, Elliott MJ. Tracheomegaly: a complication of fetal endoscopic tracheal occlusion in the treatment of congenital diaphragmatic hernia. Pediatric Radiology. 2010 May;40(5):674-80.

24. Jani J, Valencia C, Cannie M, Vuckovic A, Sellars M, Nicolaides KH. Tracheal diameter at birth in severe congenital diaphragmatic hernia treated by fetal endoscopic tracheal occlusion. Prenatal Diagnosis. 2011 Jul;31(7):699-704.

25. Cullen AB, Cooke PH, Driska SP, Wolfson MR, Shaffer TH. The impact of mechanical ventilation on immature airway smooth muscle: functional, structural, histological, and molecular correlates. Neonatology. 2006;90(1):17-27.

26. Jani JC, Nicolaides KH, Gratacos E, Valencia CM, Doné E, Martinez JM, et al. Severe diaphragmatic hernia treated by fetal endoscopic tracheal occlusion. Ultrasound in Obstetrics and Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2009 Sep;34(3):304-10.

27. Sananès N, Regnard P, Mottet N, Miry C, Fellmann L, Haelewyn L, et al. Evaluation of a new balloon for fetal endoscopic tracheal occlusion in the nonhuman primate model. Prenatal Diagnosis. 2019 Apr;39(5):403-8.

28. Basurto D, Sananès N, Verbeken E, Sharma D, Corno E, Valenzuela I, et al. New device permitting non-invasive reversal of fetal endoscopic tracheal occlusion: ex-vivo and in-vivo study. Ultrasound in Obstetrics & Gynecology. 2020 Oct;56(4):522-31.

29. Jiménez JA, Eixarch E, DeKoninck P, Bennini JR, Devlieger R, Peralta CF, et al. Balloon removal after fetoscopic endoluminal tracheal occlusion for congenital diaphragmatic hernia. American Journal of Obstetrics and Gynecology. 2017 Jul 1;217(1):78-e1-e11.

30. Morini F, Valfrè L, Bagolan P. Long-term morbidity of congenital diaphragmatic hernia: A plea for standardization. InSeminars in Pediatric Surgery 2017 Oct 1 (Vol. 26, No. 5, pp. 301-310

31. Hollinger LE, Harting MT, Lally KP. Long-term follow-up of congenital diaphragmatic hernia. InSeminars in Pediatric Surgery 2017 Jun 1 (Vol. 26, No. 3, pp. 178-184).

32. Namba F. Mesenchymal stem cells for the prevention of bronchopulmonary dysplasia. Pediatrics International. 2019;61(10):945-50.

33. DeKoninck P, Toelen J, Roubliova X, Carter S, Pozzobon M, Russo FM, et al. The use of human amniotic fluid stem cells as an adjunct to promote pulmonary development in a rabbit model for congenital diaphragmatic hernia. Prenatal Diagnosis. 2015 Sep;35(9):833-40.

34. Sadiq HF, Mantych G, Benawra RS, Devaskar UP, Hocker JR. Inhaled nitric oxide in the treatment of moderate persistent pulmonary hypertension of the newborn: a randomized controlled, multicenter trial. Journal of Perinatology. 2003 Mar;23(2):98-103.

35. Konduri GG, Solimano A, Sokol GM, Singer J, Ehrenkranz RA, Singhal N, et al. A randomized trial of early versus standard inhaled nitric oxide therapy in term and near-term newborn infants with hypoxic respiratory failure. Pediatrics. 2004 Mar 1;113(3):559-64.

36. Clark RH, Kueser TJ, Walker MW, Southgate WM, Huckaby JL, Perez JA, et al. Low-dose nitric oxide therapy for persistent pulmonary hypertension of the newborn. New England Journal of Medicine. 2000 Feb 17;342(7):469-74.

37. Neonatal Inhaled Nitric Oxide Study Group. Inhaled nitric oxide and hypoxic respiratory failure in infants with congenital diaphragmatic hernia. Pediatrics. 1997 Jun 1;99(6):838-45.

38. Kelly LE, Ohlsson A, Shah PS. Sildenafil for pulmonary hypertension in neonates. Cochrane Database of Systematic Reviews. 2017(8).

39. Cochius-den Otter S, Schaible T, Greenough A, Van Heijst A, Patel N, Allegaert K, et al. The CoDiNOS trial protocol: an international randomised controlled trial of intravenous sildenafil versus inhaled nitric oxide for the treatment of pulmonary hypertension in neonates with congenital diaphragmatic hernia. BMJ Open. 2019 Nov 1;9(11):e032122.

40. Russo FM, De Bie F, Hodges R, Flake A, Deprest J. Sildenafil for antenatal treatment of congenital diaphragmatic hernia: from bench to bedside. Current Pharmaceutical Design. 2019 Feb 1;25(5):601-8.

41. Russo FM, Benachi A, Van Mieghem T, De Hoon J, Van Calsteren K, Annaert P, et al. Antenatal sildenafil administration to prevent pulmonary hypertension in congenital diaphragmatic hernia (SToP-PH): study protocol for a phase I/IIb placenta transfer and safety study. Trials. 2018 Dec;19(1):524.