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ORIGINAL ARTICLE

Congenital diaphragmatic hernia—influence of fetoscopic tracheal occlusion on outcomes and predictors of survival

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Abstract The morbidity of infants with congenital diaphragmatic hernia (CDH) who had undergone foetal endoscopic tracheal occlusion (FETO) to those who had not was compared and predictors of survival regardless of antenatal intervention were identified. FETO was undertaken on the basis of the lung to head ratio or the position of the liver. A retrospective review of the records of 78 CDH infants was undertaken to determine the lung-head ratio (LHR) at referral and prior to birth, maximum oxygen saturation in the labour suite and neonatal outcomes. The 43 FETO infants were born earlier (mean 34 versus 38 weeks) ($p < 0.001$). They had a lower mean LHR at referral (0.65 versus 1.24) ($p < 0.001$) but not prior to birth and did not have a higher mortality than the 35 non-FETO infants. The FETO infants required significantly longer durations of ventilation (median: 15 versus 6 days) and supplementary oxygen (28 versus 8 days) and hospital stay (29 versus 16 days). Overall, the best predictor of survival was the OI in the first 24 h.

Conclusion: The FETO group had increased morbidity, but not mortality. The lowest oxygenation index in the first 24 h was the best predictor of survival regardless of antenatal intervention.

What is Known:
- *Randomised controlled trials have demonstrated that foetal endotracheal occlusion (FETO) in high risk infants with congenital diaphragmatic hernia is associated with a higher survival rate.*
- *Mortality is greater in foetuses who underwent FETO and delivered prior to 35 weeks of gestation.*

What is New:
- *Infants who had undergone FETO compared to those who had not had significantly longer durations of mechanical ventilation, supplementary oxygen and hospital stay.*
- *Regardless of antenatal intervention, the lowest oxygenation index in the first 24 h was the best predictor of survival.*

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Keywords Congenital diaphragmatic hernia · FETO · Oxygenation index · Prediction of mortality

Abbreviations

CDH	Congenital diaphragmatic hernia
CI	Confidence interval
CO_2	Carbon dioxide
ECMO	Extracorporeal membrane oxygenation
FETO	Foetal endoscopic tracheal occlusion
HFO	High frequency oscillation
iNO	Inhaled nitric oxide
LRH	Lung-head ratio
OI	Oxygenation index
$PaCO_2$	Arterial carbon dioxide level
RCT	Randomised controlled trial

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Introduction

Congenital diaphragmatic hernia (CDH), despite the introduction of such postnatal interventions as high-frequency oscillation (HFO) and inhaled nitric oxide (iNO), still has a high mortality with survival rates of between 60 and 70 % [19, 20], although certain centres have reported greater than 90 % survival [4, 8]. As a consequence, antenatal interventions including foetal endoscopic tracheal occlusion (FETO) have been undertaken in foetuses with the worst prognosis. Meta-analysis of three randomised controlled trials (RCTs) demonstrated a significantly higher survival rate following FETO, but a significantly greater rate of premature delivery [17]. We [1] previously highlighted that mortality was greater in foetuses who underwent FETO and delivered prior to 35 weeks of gestation. FETO, as above, is performed in those with the worst prognosis. We, therefore, hypothesised that CDH infants who had undergone FETO compared to those who had not would have similar survival rates but suffer greater morbidity. An aim of this study was to test that hypothesis.

Various predictors of mortality or requirement for extracorporeal membrane oxygenation (ECMO) in infants with CDH have been reported. These include being born with very low birth weight, an absent or low 5-min Apgar score [3], the oxygenation index in the first 24 h [16, 18], the SNAP-II score and highest arterial carbon dioxide level ($PaCO_2$) in the first 24 h, although the latter was not significant after multivariate adjustment [5]. Most studies, however, have not included infants who had been treated with FETO. Hence, we additionally wished to see which factors were associated with survival regardless of antenatal intervention.

Materials and methods

A retrospective review was undertaken of the case notes of infants with CDH without serious congenital or chromosomal abnormalities born at King's College Hospital (KCH) NHS Foundation Trust between 2009 and 2014. This audit was approved by the King's College Hospital NHS Foundation Trust Clinical Audit Support System and, as it was not a research project, did not require informed parental consent. KCH is a tertiary referral centre for CDH infants who might benefit from FETO; hence, our population includes CDH foetuses with the worst prognosis. Foetuses were eligible for FETO if they had a left CDH and lung to head ratio (LHR) ≤ 1.0 or a right-sided CDH with the liver in the chest. FETO occurred between 23 and 32 weeks of gestation depending on when the mothers were referred to the Fetal Assessment Centre at KCH. From 2013, if parental consent was given, CDH infants were entered into the tracheal occlusion to accelerate lung growth (TOTAL) trial which is a randomised trial (RCT) of FETO versus expected management during pregnancy in foetuses with left-sided isolated CDH. There were six infants recruited into the TOTAL trial in the time period of this study, their results have been excluded from our analyses.

FETO was performed by placing a thin-walled flexible Teflon cannula loaded with a custom-designed pyramidal trocar into the amniotic cavity through the abdominal and uterine walls and directed towards the foetal mouth. The trocar was then withdrawn and fetoscopic instruments, including an endoscope inserted. The endoscope was introduced into the foetal mouth, pharynx and epiglottis and advanced through the focal cords to identify the carina, and the catheter was positioned to deliver the balloon just above it. The procedure was usually performed under local anaesthesia [6]. Foetuses who did not undergo FETO had the same antenatal and postnatal management as the FETO group. Antenatal steroids were given to the FETO group at the time of balloon insertion if it was thought there was an increased risk of premature labour. In the non-FETO group, antenatal steroids were given if there was threatened premature labour before 34 weeks of gestation. The criteria to determine mode of delivery was the same in both groups, that is based on maternal and foetal health problems. Repair of the hernia was performed only when the infant's respiratory and cardiovascular status had stabilise, that is, they no longer required high-frequency oscillation (HFO) or inhaled nitric oxide (iNO) (see below) and no inotropes other than low-dose dopamine. Infants all received neuromuscular blocking agents during ventilation. They were initially started on time-cycled, pressure-limited ventilation but transferred to HFO if they were difficult to ventilate/oxygenate. Infants were only considered for extracorporeal membrane oxygenation under unusual circumstances [9] and, in this series, no infant was referred for ECMO. Infants were started on iNO if they required more than 50 % supplementary oxygen and had at least a 10 % difference in the pre- and post-ductal oxygen saturations as per the unit's protocol. Inotropes were commenced (dopamine first, then dobutamine added and then if necessary adrenaline) to achieve suprasystemic blood pressure in infants with evidence of pulmonary hypertension (diagnosed by differential pre/postductal saturations and/or echocardiography).

Data retrieved from the medical records included birth weight, gestational age at birth, the LHR at diagnosis and the last LHR before delivery. The maximum oxygen saturation in the delivery suite and the number in each group who had an oxygen saturation > 90 % in the delivery suite were also recorded. Oxygen saturation in the delivery suite was recorded from the right arm (i.e., preductal), and the inspired oxygen concentration increased as necessary to try and achieve an oxygen saturation of at least 90 %. Post-natally, the nurses recorded hourly on observation charts the type and amount of respiratory support and other treatments (such as inotropes and inhaled nitric oxide (iNO)) the infant received.

All infants had indwelling arterial lines from which blood gases were sampled and the results recorded on the observation charts. From those records, the lowest (i.e., best) oxygenation index in the first 24 h after birth was calculated. In addition, the highest carbon dioxide ($PaCO_2$) level in the first 24 h was noted. The durations of mechanical ventilation, supplementary oxygen and inotropic support were determined, as were the times to full enteral and full oral feeding. The type of hernia repair and the length of hospital stay were also documented.

Statistical analysis

The data were tested for normality using the Kolmogorov-Smirnov test and found to be not normally distributed. Differences between those who did and did not have FETO, therefore, were assessed for statistical significance using the Mann-Whitney *U* test or Chi-square test as appropriate. Analysis of outcomes was conducted unadjusted and after adjustment for gestational age, birth weight and antenatal steroids using logistic and linear regression analysis. Differences between infants who did and did not survive were assessed for statistical significance using the Mann-Whitney U and chi-squared tests as appropriate. The ability of variables to predict survival was assessed by using receiver operating characteristic curve (ROC) and calculating the area under the curve (AUROC). The analysis was performed using SPSS version 22.0 (SPSS, Inc., Chicago, IL).

Results

The results of 78 infants (including 43 who had undergone FETO) were analysed. Two of the 43 foetuses who underwent FETO had no change in their LHR post-FETO. Overall, five infants died in the labour suite (in the FETO group) as they could not be resuscitated. Nineteen infants in the FETO group and 13 in the non FETO group did not achieve cardiopulmonary stability and, therefore, did not undergo surgery ($p = 0.67$). Compared to non-FETO infants, the FETO infants had a lower median gestational age, birth weight and lung-to-head ratio at referral and were more likely to have been exposed to antenatal steroids and have had a patch repair (Table 1). The lung to head ratio prior to birth, however, did not differ significantly between the two groups, neither did the survival rate ($p = 0.30$). The mean duration of mechanical ventilation of the FETO infants was significantly longer than that of the non-FETO infants even after adjusting for gestational age, birth weight and antenatal steroid exposure ($p = 0.007$) (Table 2). Similarly, the duration of supplementary oxygen and the length of stay of the FETO infants were also significantly longer than that of the non-FETO infants (Table 2). The median times to full enteral feeds and full oral feeds of the FETO infants were significantly longer than those of the non-FETO infants. There was no statistically significant difference between the groups with regard to the duration of inotropic support. There were no significant differences between the two groups with regard to the lowest oxygenation index or the highest carbon dioxide level in the first 24 h.

Overall, lower gestational age, maternal age, and Apgar score at 5 min were associated with a significantly higher mortality risk (Table 3). A higher best oxygenation index and a highest carbon dioxide level in first 24 h were also associated with a significantly increased risk of mortality (Table 3). The strongest relationships with survival were observed with the oxygenation index in the first 24 h (AUROC = 0.876) and the carbon dioxide level in the first 24 h (AUROC = 0.772).

Discussion

We have demonstrated that CDH infants who underwent FETO had significantly greater morbidity than those who did not undergo FETO, but the mortality did not differ significantly between the two groups. The majority of the FETO infants underwent a patch repair compared to the minority of the non-FETO infants, highlighting that the former infants had a larger diaphragmatic defect which likely contributed to their greater morbidity [11, 14, 15]. A patch repair has been associated with a higher mortality, longer duration of supplementary oxygen and greater need for supplementary oxygen at discharge [2, 14]. The FETO group was born significantly more prematurely; indeed, their median gestational age was 34 weeks compared to 38 weeks in the non-FETO group. More premature delivery in FETO infants has been well documented and is the consequence of complications related to balloon insertion [1, 12]. Gestational age at birth has been reported in FETO infants to be predictive of the durations of ventilation and supplementary oxygen and the age at full enteral feeds [7]. If delivery, however, took place after 34 weeks of gestation, neonatal morbidity of FETO cases was comparable with that of expectantly managed cases [7]. It is thus then not surprising our FETO infants required significantly longer durations of mechanical ventilation and supplementary oxygen and had other evidence of greater morbidity than the non-FETO infants, as they were born at a significantly earlier gestational age. A greater proportion of the FETO infants, however, had been exposed to antenatal steroids, it is likely then their longer durations of mechanical ventilation and supplementary oxygen reflect pulmonary maldevelopment as well as immaturity.

The FETO infants had a significantly lower LHR at referral than the non-FETO infants, and the majority were in the worst prognostic group [13]. The LHR prior to delivery, however, did not differ significantly between the two groups, reflecting

Table 1 Patient characteristics according to treatment group

N	FETO 43	Non-FETO 35	*P* value
Maternal age	30 (26, 35)	32 (30, 34)	0.155
Antenatal steroids	70.7 % (29)	31.4 % (11)	0.002
Lung-to-head ratio at referral	0.65 (0.6, 0.8)	1.24 (1, 1.6)	<0.001
Lung-to-head ratio prior to birth	1.5 (1.3, 2.2)	1.8 (1.5, 2)	0.324
Gestational age (weeks)	34 (32, 36)	38 (37, 39)	<0.001
Birth weight (grams)	2185 (1713, 2732)	3090 (2600, 3420)	<0.001
Mode of delivery (SVD)	69.8 % (30)	62.9 % (22)	0.399
Oxygen saturation > 90 % in the delivery suite (yes)	62.5 % (25)	68.8 % (24)	0.582
Surgery (yes)	55.8 % (24)	62.9 % (22)	0.62
Type of surgical repair			
Primary	12.5 % (3/24)	68.2 % (15/22)	<0.001
Patch	87.5 % (21/24)	31.8 % (7/22)	<0.001

Data are presented as median (range) or % (*N*)

SVD spontaneous vaginal delivery

the increase in LHR resulting from the FETO procedure. There were no significant differences in the proportions of infants in the two groups who underwent surgical repair, i.e., had attained cardiopulmonary stability, which again reflects their similar LHR prior to delivery. Thus, we speculate FETO increased survival but this was at the expense of increased morbidity, as they were a worse prognostic group at referral than the non-FETO infants.

In CDH patients, inotropic support is often given to treat pulmonary hypertension. We did not find any significant difference in the duration of inotropic support between the two groups, suggesting the severity of pulmonary hypertension did not differ between FETO and non-FETO infants. In one study [10], the prenatal LHR predicted pulmonary hypertension at 1 month, but not in the longer term, and the authors suggested their results indicated remodelling of the pulmonary vasculature over time. None of the infants included in that study had undergone FETO, and our results demonstrate in such patients and in those who had not undergone FETO, it is the LHR at referral prior to delivery which differs significantly according to death or survival.

We assessed a large range of perinatal factors with regard to their ability to predict survival. Several factors gave good discrimination (Table 3). The factors that had most discrimination were the best oxygenation index and highest carbon dioxide level in the first 24 h, gestational age at birth, and the Apgar score at 5 min. The best predictor, however, was the best oxygenation index (OI) with an AUROC of 0.876. In

Table 2 Infant outcomes according to treatment group

	FETO N (43)	Non-FETO N (35)	Unadjusted *P* value	Adjusted *P* value
Duration of mechanical[a] ventilation (days)	15 (2, 24)	6 (2, 11)	0.005	0.007
Duration of post extubation[a] respiratory support (days)	6 (3, 11)	2 (2, 8)	0.02	0.038
Duration of supplementary[a] oxygen (days)	28 (4, 39)	8 (2, 15)	0.007	0.001
Best oxygenation index in first 24 h	6.4 (2.8, 13.2)	3.8 (2.5-7.2)	0.575	0.089
Highest carbon dioxide level in first 24 h (kPa)	7.1 (5.5,10)	6.5 (5.5, 9)	0.579	0.632
Length of hospital stay (days)	29 (3, 59)	16 (2, 26)	0.023	0.013
Time to full enteral feeding[a] (days)	26 (22,31)	16 (12, 21)	<0.001	0.03
Time to full oral feeding[a] (days)	42 (31, 57)	22 (14, 31)	<0.001	0.04
Duration of inotropic support (days)	4 (2, 10)	3 (2,5)	0.044	0.06
Time to surgery (days)[a]	6 (5, 9)	5 (3, 6)	0.013	0.285
Survival	44.2 %	63 %	0.1	0.30

Results are expressed as median (interquartile range)

[a] Data shown for survivors only

Table 3 Factors associated with survival

	Survived $N = 41$	Not survived $N = 37$	*P* value	AUROC
Gestational age (weeks)	38 (35, 39)	34. 4 (32.6, 37.1)	<0.001	0.752
Maternal age (years)	32 (31, 37)	29 (25, 33)	0.001	0.728
Antenatal steroids	18 (44 %)	22 (59.5 %)	0.065	0.637
Mode of delivery (SVD)	28 (68.3 %)	24 (64.9 %)	0.199	0.519
Birth weight (grams)	2785 (2200, 3146)	2305 (1665, 2917)	0.017	0.658
$SPO_2 > 90$ % in delivery suite (yes)	33 (80.5 %)	16 (47 %)	0.003	0.667
Best oxygenation index in the first 24 h	2.85 (2.5,3.56)	15.4 (7.7,34.8)	<0.001	0.876
Highest CO_2 first 24 h (kPa)	5.95 (5.24,6.97)	9 (6.7,11.1)	<0.001	0.772
LHR at diagnosis	1 (0.64,1.3)	0.8 (0.6,0.9)	0.041	0.634
LHR prior to birth	1.84 (1.4,2.2)	1.5 (1.2,1.9)	0.038	0.644

Data are demonstrated as median interquartile range or *N* (%)

a previous study [16], the best oxygenation index in the first 24 h was shown to be a better predictor of survival than birth weight or gestational age in FETO and non-FETO infants.

This study has strengths and some limitations. We report a consecutive series of CDH infants, other than six infants who were entered into the TOTAL trial. The infants underwent management in a single centre with a standardised protocol. The number of infants delivered in the study period indicates KCH is a "high volume" centre. The data were collected retrospectively, and certain information was missing, for example, the mode of delivery and birth weight of the infants who did not survive to the neonatal unit, but as this only applied to five infants, we do not feel this impacted on our overall results. The study population reported received FETO on the basis of the LHR or the position of the liver; thus, we are not able to compare infants who had a low LHR and did undergo FETO with those that did. As shown in Table 1, all those who had a low LHR underwent FETO.

In conclusion, CDH infants who underwent FETO compared to those who did not had greater morbidity, but not mortality. This likely reflects that they were born significantly more prematurely and further emphasises the need to reduce premature delivery following FETO. In both FETO and non-FETO infants, the best OI in the first hours after birth gave the greatest discrimination with regard to survival.

Author's contribution KA and AG designed the study; KA, PB, SP and GA collected the data; MO, JP and KA undertook the statistical analysis. All authors were involved in producing the manuscript.

Compliance and ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent This audit was approved by the King's College Hospital NHS Foundation Trust Clinical Audit Support Committee and, as it was not a research project, it did not require informed parental consent.

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Conflict of interest The authors declare that they have no conflict of interest.

References

1. Ali K, Grigoratos D, Cornelius V, Davenport M, Nicolaides K, Greenough A (2013) Outcome of CDH infants following fetoscopic tracheal occlusion—influence of premature delivery. J Pediatr Surg 48:1831–1836
2. Brindle ME, Brar M, Skarsgard ED, Canadian Pediatric Surgery Network (CAPSNet) (2011) Patch repair is an independent predictor of morbidity and mortality in congenital diaphragmatic hernia. Pediatr Surg Int 27:969–974
3. Brindle ME, Cook EF, Tibboel D, Lally PA, Lally KP, Congenital Diaphragmatic Hernia Study Group (2014) A clinical prediction rule for the severity of congenital diaphragmatic hernias in newborns. Pediatrics 134:e413–e419
4. Boloker J, Bateman DA, Wung JT, Stolar CJ (2002) Congenital diaphragmatic hernia in 120 infants treated consecutively with permissive hypercapnea/spontaneous respiration/elective repair. J Pediatr Surg 37:357–366
5. Coleman AJ, Brozanski B, Mahmood B, Wearden PD, Potoka D, Kuch BA (2013) First 24-h SNAP-II score and highest $PaCO_2$ predict the need for ECMO in congenital diaphragmatic hernia. J Pediatr Surg 48:2214–2218
6. Deprest J, Jani J, Gratacos E, Vandecruys H, Naulaers G, Delgado J, Greenough A, Nicolaides K, FETO Task Group (2005) Fetal intervention for congenital diaphragmatic hernia: the European experience. Semin Perinatol 29:94–103
7. Doné E, Gratacos E, Nicolaides KH, Allegaert K, Valencia C, Castañon M, Martinez JM, Jani J, Van Mieghem T, Greenough A, Gomez O, Lewi P, Deprest J (2013) Predictors of neonatal morbidity in fetuses with severe isolated congenital diaphragmatic hernia

undergoing fetoscopic tracheal occlusion. Ultrasound Obstet Gynecol 42:77–83
8. Downard CD, Jaksic T, Garza JJ, Dzakovic A, Nemes L, Jennings RW, Wilson JM (2003) Analysis of an improved survival rate for congenital diaphragmatic hernia. J Pediatr Surg 38:729–732
9. ELSO Organization. ELSO Registry Report - International Summary 2015 July. Available from: https://www.elso.org/Registry/Statistics/InternationalSummary.aspx
10. Garcia AV, Fingeret AL, Thirumoorthi AS, Hahn E, Leskowitz MJ, Aspelund G, Krishnan US, Stolar CJ (2013) Lung to head ratio in infants with congenital diaphragmatic hernia does not predict long term pulmonary hypertension. J Pediatr Surg 48:154–157
11. Jancelewicz T, Vu LT, Keller RL, Bratton B, Lee H, Farmer D, Harrison M, Miniati D, Mackenzie T, Hirose S, Nobuhara K (2010) Long-term surgical outcomes in congenital diaphragmatic hernia: observations from a single institution. J Pediatr Surg 45:155–160
12. Jani JC, Nicolaides KH, Gratacos E, Valencia CM, Done E, Martinez JM, Gucciardo L, Cruz R, Deprest JA (2009) Severe diaphragmatic hernia treated by fetal endoscopic tracheal occlusion. Ultrasound Obstet Gynecol 34:304–310
13. Jani JC, Nicolaides KH, Gratacós E, Vandecruys H, Deprest JA, FETO Task Group (2006) Fetal lung-to-head ratio in the prediction of survival in severe left-sided diaphragmatic hernia treated by fetal endoscopic tracheal occlusion (FETO). Am J Obstet Gynecol 195:1646–1650
14. Lally KP, Lasky RE, Lally PA, Bagolan P, Davis CF, Frenckner BP, Hirschl RM, Langham MR, Buchmiller TL, Usui N, Tibboel D, Wilson JM, Congenital Diaphragmatic Hernia Study Group (2013) Standardized reporting for congenital diaphragmatic hernia—an international consensus. J Pediatr Surg 48:2408–2415
15. Muratore CS, Utter S, Jaksic T, Lund DP, Wilson JM (2001) Nutritional morbidity in survivors of congenital diaphragmatic hernia. J Pediatr Surg 36:1171–1176
16. Ruttenstock E, Wright N, Barrena S, Krickhahn A, Castellani C, Desai AP, Rintala R, Tovar J, Till H, Zani A, Saxena A, Davenport M (2015) Best oxygenation index on day 1: a reliable marker for outcome and survival in infants with congenital diaphragmatic hernia. Eur J Pediatr Surg 25:3–8
17. Shan W, Wu Y, Huang G, Zeng L, Yuan M, Huang L, Xiang B, Jiang X (2014) Foetal endoscopic tracheal occlusion for severe congenital diaphgramatic hernia—a systemic review and meta-analysis of randomized controlled trials. J Pak Med Assoc 64:686–689
18. Sinha CK, Islam S, Patel S, Nicolaides K, Greenough A, Davenport M (2009) Congenital diaphragmatic hernia: prognostic indices in the fetal endoluminal tracheal occlusions era. J Pediatr Surg 44:312–316
19. Sola JE, Bronson SN, Cheung MC, Ordonez B, Neville HL, Koniaris LG (2010) Survival disparities in newborns with congenital diaphragmatic hernia: a national perspective. J Pediatr Surg 45:1336–1342
20. van den Hout L, Schaible T, Cohen-Overbeek TE, Hop W, Siemer J, van de Ven K, Wessel L, Tibboel D, Reiss I (2011) Actual outcome in infants with congenital diaphragmatic hernia: the role of a standardized postnatal treatment protocol. Fetal Diagn Ther 29:55–63