Original Articles

Outcome of CDH infants following fetoscopic tracheal occlusion — influence of premature delivery☆,☆☆

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Abstract

Purpose: To evaluate the mortality and morbidity of infants with congenital diaphragmatic hernia who had undergone fetal endoscopic tracheal occlusion (FETO) and whether this was influenced by premature birth.

Methods: The gestational age at delivery, lung–head ratio (LHR) pre and post FETO, neonatal outcomes, and respiratory, gastro-intestinal, neurological, surgical, and musculoskeletal problems at follow up of consecutive infants who had undergone FETO were determined. Elective reversal of FETO was planned at 34 weeks of gestation.

Results: The survival rate of the 61 FETO infants was 48%, with 84% delivered prematurely. Thirty-one delivered <35 weeks of gestation. Their survival rate was 18%. Twenty-three of 24 infants who had emergency balloon removal were born <35 weeks of gestation. Survival was related to gestational age at delivery (OR 0.55, 95% CI 0.420, 0.77, p<0.001) and the duration of FETO (OR 0.73, 95% CI 0.59, 0.91, p<0.005). Infants born prior to 35 weeks of gestation compared to those born at ≥35 weeks required a longer duration of ventilation (median 45 days versus 12 days, p<0.001), and a greater proportion had surgery for gastro-oesophageal reflux (50% versus 9%, p=0.011).

Conclusion: These results emphasize the need to reduce premature delivery following FETO.

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Congenital diaphragmatic hernia (CDH) is a common congenital anomaly with an incidence of approximately 1 in 3000 [1]. Despite the introduction of a variety of postnatal interventions including high frequency oscillation (HFO), inhaled nitric oxide (iNO) and extracorporeal membrane oxygenation (ECMO), the survival rate of CDH infants remains between 60% and 70% [2–4]. As a consequence, attention has focused on developing antenatal interventions

for fetuses predicted to have the worst outcome [5]. In a non-randomised study [5], fetal endoscopic tracheal occlusion (FETO), which involves placing a balloon in the trachea, improved the survival of the selected fetuses with a left CDH from 24.1% to 49.1% and in fetuses with a right CDH from 0% to 35.3%.[6] FETO has, however, been associated with an increased risk of premature delivery [6] and premature delivery in "non FETO" CDH infants has been associated with a lower survival rate [7,8]. In one series [7], the survival rate in CDH infants delivered at term was 64%, whereas in those born prematurely it was only 35%. In another series [8] the respective survival rates were 73.1% and 53.5%. The aims, therefore, of this study were to determine the impact of premature delivery of the survival rate of CDH infants who had undergone FETO and whether premature delivery was associated with increased morbidity, as such data would inform counselling of prospective parents.

1. Materials and methods

A retrospective review was undertaken of all infants with CDH without other serious congenital anomalies born at King's College Hospital (KCH) NHS Foundation Trust who had undergone FETO during a six-year period from 2004 to 2009. Infants were identified from the neonatal and surgical databases. 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 fetal mouth. The trocar was then withdrawn and fetoscopic instruments, including an endoscope, inserted. The endoscope was introduced into the fetal 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 initially performed under general anaesthetic but subsequently combined spinal–epidural anaesthesia and more usually local anaesthesia [5]. FETO occurred between 23 and 32 weeks depending on when the mothers were referred to the fetal assessment unit at KCH. Fetuses underwent FETO if they had a lung to head ratio (LHR) ≤ 1.0. The aim was to electively puncture the balloon at 34 weeks, but in practise this occurred between 33 and 37 weeks. Women who went into premature labour were given oral nifedipine or had GTN patches. In those delivering before elective balloon removal, the balloon was removed as an emergency procedure either shortly before or immediately after delivery by one of the fetal medicine team. Infants with CDH during the six year period followed the same protocols of postnatal management. In particular, repair of the hernia was performed only when the infant's respiratory and cardiovascular status had stabilised. Four paediatric surgeons undertook CDH repair and all had prior experience. Infants had a combined surgical and neonatal follow up at three to six monthly intervals, unless the infant's clinical condition dictated otherwise.

Data retrieved from the medical records included birth weight, gestational age at birth, the lung–head ratio (LHR) pre FETO and the last LHR before delivery. The LHR was also expressed as the observed to expected LHR using a previously constructed reference range based on gestational age [9]. In addition the duration of mechanical ventilation, use of high frequency oscillation (HFO), inhaled nitric oxide (iNO) and/or inotropic support, time to surgery and type of diaphragmatic repair were ascertained. At follow up, respiratory, gastrointestinal, neurological, surgical (ie recurrence of the hernia) and musculoskeletal problems were recorded. Growth failure was diagnosed if the infant's weight was below the second centile for age and/or crossed downwards two centiles. Gastroesophageal (GO) reflux was diagnosed if the infant had signs of reflux, vomiting and feed intolerance. Radiological investigations were performed in those unresponsive to medical management for gastro-oesophageal reflux, before they underwent surgical intervention (fundoplication). Reactive airway disease was diagnosed if the infant had recurrent wheeze requiring bronchodilator and/or steroid therapy. Audiological screening was performed for all infants before discharge from the neonatal intensive care unit. Delay in motor milestones, defined as abnormalities of muscle tone, movement and/or motor skill acquisition was determined as part of the out-patient follow up by consultant paediatricians during infancy. The infants were seen in joint paediatric and paediatric surgical clinics, but did not routinely undergo Bayley or Griffith's testing. Prognostic indices of survival in 51 of the infants have been previously reported [10].

1.1. Analysis

Differences between groups were assessed for statistical significance using a chi-squared test, Fisher's exact test or an independent t-test as appropriate. Logistic regression was used to examine the relationship between binary outcomes and gestational age, where gestational age was included in the model as a continuous variable. Kaplan–Meier survival estimates were plotted. Time to event analysis was calculated for survival, duration of ventilation and time to surgical intervention, if no event occurred before the end of the study follow up (12 months), observation for outcomes were censored. Differences in time to event curves between groups were analysed using the log rank test. All calculations were performed in Stata version 11.2 (StataCorp LP, Texas).

2. Results

Sixty-one CDH infants who were delivered at KCH in the six year period underwent FETO (Table 1), 84% delivered prematurely. There were no survivors born prior to 33 weeks of gestational age (Table 2). In 37 cases the balloon was removed

Table 1 Demographics and short term outcomes of the study population.

n	61
Gestational age at delivery (weeks)	34 (24–40)
Birth weight (kg)	2.24 (0.55–3.80)
Gender (male)	34 (56%)
Pre-FETO LHR	0.6 (0.3–1.2)
Last LHR	1.9 (0.5–3.6)
Time to surgical repair (days) [a]	4 (2–12)
Duration of ventilation (days) [a]	12 (0–70)
Mode of delivery	
Vaginal delivery/instrumental	48 (79)
Caesarian section	13 (21)
Ventilation mode (52) [a]	
Conventional	36 (69)
HFOV	16 (31)
Type of repair (39) [a]	
Primary repair	11 (28)
Patch repair	28 (72)
Nitric oxide (53) [a]	27 (51)
Inotropic support (53) [a]	53 (100)

Data are reported as median (range) or n (%).

  [a] Data were not available for all infants as some infants died in the labour ward or shortly after admission to the neonatal unit. The numbers in parentheses indicate the numbers for whom data were available.

Fig. 1 Kaplan Meier plot of survival. - - - < 35 weeks. —— ≥ 35 weeks.

electively, 18 of the 37 infants delivered in the subsequent week. In 24 cases the balloon was removed as an emergency procedure, in 23 cases delivery occurred before 35 weeks of gestation. None of the infants underwent an EXIT procedure. Overall, the survival rate was 48%. None of the infants in this series underwent extracorporeal membrane oxygenation.

There was no significant difference in the gestation at which FETO was performed between those who survived and did not survive (median 26, range 23–32 weeks versus 25, range 23–31 weeks) (p=0.4). Nine infants died in the labour suite. In all cases, the balloon had been successfully removed. Survival rates were lower in infants born prematurely (43% versus 70%), but particularly so in those born prior to 35 weeks of gestation compared to those born at 35 weeks of gestation or greater (18% versus 82%, p<0.001) (Table 2; Fig. 1) and amongst those who had

Table 2 Survival at discharge by gestational age.

Weeks	Total number born	Survival to discharge
≤ 32	16	0
33	8	3
34	9	3
35	12	11
36	6	5
37	2	1
38	3	2
39	3	2
40	2	2

Data are displayed as the number of infants.

emergency rather than elective removal of the balloon (13% versus 70%, p=0.0001). As a consequence, comparison was made of the short and long term outcomes of those born prior to 35 weeks to those born at 35 weeks of gestation or greater.

There were no significant differences in the pre FETO LHR results of those who did and did not deliver before 35 weeks of gestation, but the observed:expected LHR was significantly lower in those who were born before 35 weeks of gestational age (p=0.011) (Table 3). The last LHR documented before delivery and expressed as the observed: expected ratio, however, was significantly lower (p=0.005, p=0.004 respectively), as was the change in LHR (p=0.01, p=0.034 respectively) in the infants born prior to 35 weeks of gestation compared to those born at ≥ 35 weeks of

Table 3 LHR results (displayed as means) according to gestational age at delivery.

	<35 weeks	≥35 weeks	Mean difference between the groups	p
Pre FETO	0.62	0.68	0.06	0.183
Pre FETO LHR expressed as observed: expected	0.16	0.21	0.05	0.011
Last LHR	1.66	2.15	0.49	0.005
Last LHR expressed as observed: expected	0.39	0.51	0.12	0.004
Change in LHR (ie last LHR − pre FETO	1.04	1.47	0.43	0.010
Change in LHR expressed as observed: expected	0.22	0.30	0.08	0.034

The results are expressed as means.

gestation (Table 3). The median duration of tracheal occlusion was significantly shorter in those infants born prior to 35 weeks of gestation (median 5 (range 1–10) weeks versus median 8 (range 3–11) weeks, $p < 0.001$).

The infants born below 35 weeks gestation had a median birth weight of 1.94 (range 0.6–2.7) kg and those born at or after 35 weeks gestation had a median birth weight of 2.56 (range 1.99–3.8) kg ($p = 0.0001$). Twenty infants (65%) born prior to 35 weeks were male and 12 infants (40%) born ≥ 35 weeks of gestation were male ($p = 0.62$). A patch repair was required in ten (32%) of the infants born before 35 weeks and in 18 (60%) of those born at or after 35 weeks of gestation ($p = 0.574$). The duration of ventilation was longer (median 45 versus 12) days, $p < 0.001$) and surgery occurred later (median five versus four days, $p < 0.001$) in infants born at less than 35 weeks of gestation.

Twenty nine infants, six born prior to 35 weeks survived to follow-up (Table 4). All infants were followed for a minimum of 12 months, maximum of five years. Six of the 29 survivors had symptoms related to upper airway disease at follow up (stridor/exercise induced barking cough), three underwent bronchoscopy because of the severity of their symptoms and were diagnosed as having tracheomalacia.

Table 4 Outcomes overall and by gestational age for infants who survived (n=29).

n	Overall	<35 weeks	≥35 weeks	p
	29	6	23	
Hernia recurrence (n=28)	7 (25)	3 (50)	4 (18)	0.144
Hospitalized with LRTI (n=28)	11 (39)	2 (33)	9 (41)	0.999
Reactive airways disease (n=28)	5 (18)	2 (33)	3 (14)	0.285
Antireflux medications (n=27)	9 (33)	3 (50)	6 (29)	0.367
Surgery for GO reflux (n=27)	4 (15)	3 (50)	1 (4.8)	0.025
Growth failure (n=28)	7 (25)	3 (50)	4 (18)	0.144
Delayed motor milestones (n=28)	1 (1.0)	1 (17)	0 (0.0)	0.214
Thoracic or spinal deformity (n=28)	10 (36)	3 (50)	7 (32)	0.634
Hearing loss (n=28)	2 (7.1)	1 (17)	1 (5)	0.389
Upper airway symptoms at follow up (n=29)	6 (21)	1 (17)	5 (22)	0.999

Data are shown as n (%).

Tracheostomy was performed for two patients. The only significant difference in long term outcomes between the two groups was that a greater proportion of the infants born prior to 35 weeks of gestation had surgery for gastro-oesophageal reflux ($p = 0.025$) (Table 4). A greater proportion of those who underwent emergency rather than elective removal of the balloon underwent surgery for gastro-oesophageal reflux ($p = 0.005$).

Logistic regression analysis demonstrated that survival was significantly related to gestational age at delivery (odds ratio (OR) 0.55, (95% CI 0.40, 0.77) $p < 0.001$)) and the duration of FETO (OR 0.73 (95% CI 0.59, 0.91) $p < 0.005$)).

3. Discussion

We have demonstrated that the majority of CDH infants who had undergone FETO delivered prematurely and survival in those born prematurely compared to those born at term was significantly lower, particularly if delivery was prior to 35 weeks of gestation. The influence of premature delivery on survival rates of CDH infants then is similar to that reported in "non FETO" CDH infants [7,8]. FETO, however, is only performed in fetuses predicted to have a poor prognosis. The LHR prior to the FETO procedure predicts postnatal survival [11], with survival increasing from 17% with an LHR of 0.4–0.5 to 62% with an LHR of 0.6–0.7. In this series, there was no significant difference in the mean LHR ratio pre FETO of those born <35 or ≥ 35 weeks of gestation, both groups had a mean LHR of 0.6–0.7. The LHR, however, changes with gestational age, hence we also expressed the results as the observed: expected LHR [9]. The comparison of those results showed the infants born prior to 35 weeks of gestation had a significantly lower observed:expected LHR and might, therefore, have had more severe pulmonary hypoplasia which may have contributed to their increased mortality. The infants born ≥ 35 weeks of gestation had a greater change in LHR and their last LHR was significantly higher than that of the infants born <35 weeks of gestation. The infants born ≥ 35 weeks of gestation also had tracheal occlusion for a significantly longer period, this likely also explains their better survival rate. In a nitrofen rat model, prolonged (2 and 2.5 days) compared to short (one day) tracheal occlusion resulted in higher lung–body-weight ratios, more complex airway architecture and less muscularised pulmonary arteries [12]. Regression analysis demonstrated that survival was significantly related to the gestational age at delivery and the duration of FETO.

In 24 cases, emergency balloon removal was required, 23 of the 24 infants were born prior to 35 weeks of gestational age. Not surprisingly then, comparison of the outcomes of those who had emergency compared to elective balloon removal highlighted both mortality and morbidity at follow up (a greater proportion have surgery

for gastro-oesophageal reflux) were significantly higher in those requiring emergency balloon removal similar to the poorer outcomes of infants born prior to 35 weeks of gestation. Emergency balloon removal was undertaken when premature labour had occurred before the planned elective removal. Hence, those results further emphasize the importance of reducing premature delivery in CDH cases who have undergone FETO.

The infants born prior to 35 weeks of gestation also suffered greater morbidity; they required a longer duration of ventilation and more had surgery for gastro-oesophageal reflux. Overall, 31% of the infants received anti-reflux medication and 21% had surgery for GOR. All the latter group of infants had remained symptomatic despite medical investigation and had reflux confirmed by imaging, hence we feel this does suggest they had severe reflux. This is in keeping with gastro-oesophageal reflux or some form of foregut dysmotility being reported in 45%–90% of a series of CDH infants [13]. The incidence of gastro-oesophageal reflux has been correlated with the defect size and need for patch repair [14]. Patch repair is also significantly associated with other adverse surgical outcomes, including operative small bowel obstruction, hernia recurrence and early chest wall deformity [15]. Hernia recurrence has been reported in 8%–50% of CDH patients, especially in those with a patch repair [16]. The majority of infants in this study had undergone a patch repair and there was hernia recurrence in 25% of the survivors.

Significant developmental delay and behaviour disorders have been reported in CDH infants, particularly in those infants with a large diaphragmatic defect or who had needed ECMO [13]. Follow up of survivors of CDH in one series [17] demonstrated neurodevelopmental delay in 12.8%, musculoskeletal sequelae in 15.3% and recurrence of hernia in 10.2% [17]. Ten percent of the survivors in this series, none of whom had had ECMO, had delayed motor milestones in keeping with previous data [17]. A limitation of this study was that formal developmental assessment, that is undertaking Bayley or Griffith's testing was not undertaken as part of this study, but all the infants were assessed by consultant paediatricians at out-patient follow up. Two infants suffered hearing loss, sensorineural hearing loss has been reported in CDH survivors regardless of whether they required ECMO [13]. Severe hypoxemia, prolonged ventilation and ECMO are risk factors for sensorineural hearing loss, but it may also be related to treatments for respiratory failure such as hyperventilation, ototoxic medications and/or neuromuscular blockade [13].

Tracheal problems have been reported in CDH infants who underwent FETO [18,19]. Comparison of 37 infants who underwent FETO and 74 preterm and term neonates with no congenital lung anomalies revealed the CDH group had significantly greater tracheal diameter on chest x-rays obtained within 48 h of birth [20]. At follow up (median 22, (range 1–70) months), five of 24 CDH infants had an effort-induced barking cough [20]. The duration of tracheal occlusion and the pre FETO LHR were significant predictors of tracheal diameter [20]. In this series, we did not see any significant difference in the occurrence of upper airway symptoms between those delivering prior to or after 35 weeks of gestation, despite the latter group being exposed to a longer duration of tracheal occlusion.

In infants with CDH who had been treated by FETO, premature delivery was common and associated with significantly greater mortality, with no survivors born before 33 weeks of gestation. Survival was also significantly related to the duration of FETO. These results emphasize the need to reduce premature delivery following FETO and are useful to inform counselling of parents.

Acknowledgment

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