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ORIGINAL ARTICLE

# Outcomes of infants with congenital diaphragmatic hernia by side of defect in the FETO era

**Kamal Ali[1] · Theodore Dassios[1,2] · Syed Abdul Khaliq[1] · Emma E. Williams[2] · Kentaro Tamura[1,3] · Mark Davenport[4] · Anne Greenough[1,2,5,6]**

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## Abstract

**Purpose** To compare the outcomes of infants with a right (RCDH) versus a left-sided (LCDH) congenital diaphragmatic hernia (CDH) and whether these differed according to whether the infants had undergone fetoscopic tracheal occlusion (FETO).

**Methods** Demographics, the type of surgical repair, preoperative and postoperative courses and respiratory, gastrointestinal, surgical and skeletal morbidities at follow-up were compared between infants with a RCDH or LCDH. A sub-analysis was undertaken in those who had undergone FETO.

**Results** During the study period, there were 167 infants with a LCDH and 24 with a RCDH; 106 underwent FETO (15 RCDH). Overall, the need for inhaled nitric oxide ($p=0.036$) was higher in the RCDH group and, at follow-up, infants with RCDH were more likely to have a hernia recurrence ($p=0.043$), pectus deformity ($p=0.019$), scoliosis ($p=0.029$) and suffer chronic respiratory morbidity ($p=0.001$). There were, however, no significant differences in short term or long term outcomes (hernia recurrence ($p=0.237$), pectus deformity ($p=0.322$), scoliosis ($p=0.0174$) or chronic respiratory morbidity ($p=0.326$)) between infants with a right or left sided CDH who had undergone FETO.

**Conclusion** Overall, infants with a RCDH compared to those with a LCDH had greater long-term morbidity, but not if they had undergone FETO.

**Keywords** Congenital diaphragmatic hernia · Survival · Follow-up · Hernia recurrence

## Introduction

Congenital diaphragmatic hernia (CDH) occurs in approximately 1 in 2500 live births [1, 2]. Left sided CDH (LCDH) patients comprise the majority of cases, with right-sided CDH (RCDH) accounting for approximately 15–20% of cases [3–5]. The survival of infants with RCDH has been reported as higher [6], more frequently lower [5–8] or similar to LCDH [9]. This variation in the survival of RCDH can be explained by the different periods during which the studies were conducted, as well as by the different population of patients with RCDH considered, that is, pre and postnatal cases versus only postnatal cases [6]. Indeed, postnatally diagnosed CDH infants have a much better prognosis than those diagnosed antenatally [7]. Since the introduction of antenatal interventions such as fetal tracheal occlusion (FETO), survival of infants with severe diaphragmatic hernias has increased [10, 11], but affected infants are more likely to deliver prematurely, have increased short term morbidity [12] and suffer greater long-term complications [13].

✉ Anne Greenough
anne.greenough@kcl.ac.uk

1 Neonatal Intensive Care Centre, 4th Floor Golden Jubilee Wing, King's College Hospital NHS Foundation Trust, Denmark Hill, London SE5 9RS, UK

2 Women and Children's Health, School of Life Course Sciences, Faculty of Life Sciences and Medicine, King's College London, London, UK

3 Division of Neonatology, Maternal and Perinatal Centre, Toyama University Hospital, Toyama, Japan

4 Department of Paediatric Surgery, King's College Hospital NHS Foundation Trust, London, UK

5 The Asthma UK Centre for Allergic Mechanisms of Asthma, King's College London, London, UK

6 NIHR Biomedical Centre at Guy's and St Thomas NHS Foundation Trust and King's College London, London, UK

Whether the long-term outcomes in such populations differ between *R* and *L* sided CDH infants has rarely been reported. The aim of this study was to compare short and long-term outcomes of CDH infants with right sided versus left-sided defects who underwent standardized treatment and follow-up at a single institution at which FETO was performed [14]. In addition, we were interested to determine if the outcomes differed according to side of defect in those infants who had undergone FETO.

## Methods

A retrospective review was undertaken of consecutive infants with CDH, but without other serious congenital or chromosomal abnormalities born at King's College Hospital (KCH) NHS Foundation Trust between 2004 and 2018. A serious congenital abnormality was defined as one which required intervention in the immediate neonatal period, i.e., a major cardiac abnormality and a serious congenital abnormality was defined as one which was incompatible with a normal life span. The 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. The Health Research Authority Toolkit of the National Health System, United Kingdom confirmed that the study would not be considered as research and would not need regulatory approval by a research ethics committee.

KCH is a tertiary referral centre for CDH infants who might benefit from FETO. Fetuses were eligible for FETO if they had a left CDH and lung to head ratio (LHR) $\leq 1.0$ 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. All infants were initially started on time-cycled, pressure-limited ventilation, but transferred to high frequency oscillation (HFO) if they were difficult to ventilate or oxygenate. Infants were started on inhaled nitric oxide (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 if necessary adrenaline) to achieve suprasystemic blood pressure in infants with evidence of pulmonary hypertension (diagnosed by differences in the pre and post-ductal saturations and/or echocardiography). Repair of the hernia was performed only when the infant's respiratory and cardiovascular status had stabilized, that is, they no longer required HFO or iNO and no inotropes other than low-dose dopamine.

The patient demographics, the LHR at diagnosis, details of surgical repair and postoperative course were obtained from the medical records. After hospital discharge, all patients were followed in paediatric surgical and neonatal clinics at 3–6month intervals for at least 1 year. If no active issues were noted, patients were seen annually at the paediatric surgical clinic. Those born before 2014 had had at least 4 years of follow-up. There were no significant differences in the length of follow up between those with a right or left sided CDH. The respiratory, nutritional, and musculoskeletal (scoliosis or pectus excavatum) morbidities of each patient were identified from the clinic records. Chronic respiratory morbidity was diagnosed if the patient had a cough which persisted for more than 4 weeks or had had more than two respiratory admissions as documented in the medical records. Such children were followed up in the paediatric respiratory clinic. The time to full enteral feeds was documented. Pectus deformity was diagnosed if there was depression of the sternum and lower costal cartilages as indicated in the medical records.

### Statistical analysis

The data were tested for normality using the Kolmogorov–Smirnov test and found not to be normally distributed. Therefore, differences in the results of the right and left sided CDH patients were assessed for statistical significance using the Mann–Whitney *U* test or $\chi^2$ test as appropriate. The analysis was performed using SPSS version 22.0 (SPSS, Inc., Chicago, IL, USA).

## Results

One hundred and sixty-seven infants with LCDH and 24 infants with RCDH were born during the study period. All were diagnosed antenatally and 106 infants had undergone FETO (15 RCDH). There were no statistically significant differences in the gestational age at birth ($p=0.855$), birth weight ($p=0.989$) and gender ($p=0.665$) between infants with right or left sided CDHs (Table 1). The lung to head ratio at diagnosis did not differ significantly between the two groups, neither did survival (60% vs 50%, $p=0.375$) (Table 1).

Overall, neither, the time to operative repair, the median duration of mechanical ventilation nor the time to reach full enteral feeds differed significantly between the groups (Table 2). Overall, the use of nitric oxide was significantly more common in infants with RCDH ($p=0.036$). The need for high frequency oscillatory ventilation, patch repair of the diaphragmatic defect and postoperative mortality did not differ significantly between the two groups (Table 2). There was no statistically significant difference in the length of hospital stay between infants with left and right-sided CDH ($p=0.372$).

**Table 1** Demographics of the infants according to the side of the hernia

| | LCDH (167) | RCDH (24) | *P* value |
|---|---|---|---|
| Gestational age (weeks) | 36 (34–39) | 36 (34–38) | 0.855 |
| Birth weight (grams) | 2590 (2160–3120) | 2670 (2270–2890) | 0.989 |
| Sex (male) | 92 (55%) | 12 (50%) | 0.665 |
| LHR at diagnosis | 0.7 (0.43–1.05) | 0.7 (0.5–0.8) | 0.692 |
| One minute Apgar score | 6 (4–8) | 4 (2–5) | 0.005 |
| Five minute Apgar score | 7 (5–9) | 7 (5–9) | 0.842 |
| FETO | 91 (54%) | 15 (63%) | 0.532 |

Data are presented as median (interquartile range) or number (%)

**Table 2** Outcomes of infants according to side of the hernia

| | Left CDH | Right CDH | *P* value |
|---|---|---|---|
| *n* | 167 | 24 | |
| Survival | 101 (60%) | 12 (50%) | 0.375 |
| Duration of ventilation (days) | 9 (3–16) | 5 (2–16) | 0.402 |
| HFOV | 75 (45%) | 14 (58%) | 0.162 |
| Nitric oxide | 90 (54%) | 19 (79%) | 0.036 |
| Time to full feeds (days) | 20 (14–25) | 24 (21–34) | 0.082 |
| Surgical repair of CDH | 117 (70%) | 13 (54%) | 0.157 |
| Time to surgery (days) | 4 (3–6) | 5 (4–6) | 0.474 |
| Patch repair | 57/115 (50%) | 9/13 (69%) | 0.245 |
| Post-operative mortality | 16/117 (14%) | 1/13 (8%) | 0.544 |
| Length of stay (days) | 24 (3–40) | 19 (2–41) | 0.372 |

Data are expressed as number (%) or median (interquartile range)

Long-term outcome data were available for 94 LCDH (93% of the survivors) and 12 RCDH (100% of the survivors) infants. Recurrence of the hernia was more common in RCDH infants ($p = 0.043$). At follow-up, infants with a RCDH were more likely to have pectus deformities ($p = 0.019$), scoliosis ($p = 0.029$) and chronic respiratory morbidity ($p = 0.001$) (Table 3).

Neither the short (Table 4) nor long term (Table 5) outcomes of infants who had undergone FETO differed significantly according to the side of the defect.

## Discussion

We have shown that infants overall with RCDH had greater long-term respiratory, surgical and musculoskeletal morbidities than those with a LCDH. Importantly, we, however, found no significant differences regarding short and long term outcomes regarding side of defect in those infants who had undergone FETO. To our knowledge, this is the first study that reports long-term outcomes of RCDH compared to LCDH following antenatal fetal tracheal occlusion.

Overall, the RCDH infants had a higher recurrence of the hernia at follow up. This is likely due to the large size of the defect in the RCDH infants, as the majority of patients required a patch repair. An increased risk of hernia recurrence in RCDH compared to LCDH has been reported by others [15, 16]. In one study, 9% of infants

**Table 3** Long- term outcomes of infants according the to the side of the hernia

| | LCDH | RCDH | *P* value |
|---|---|---|---|
| *n* | 94 | 12 | |
| Hernia recurrence | 11 (12%) | 4 (33%) | 0.043 |
| Pectus deformity | 24 (26%) | 7 (58%) | 0.019 |
| Scoliosis | 6 (6%) | 3 (25%) | 0.029 |
| Fundoplication | 10 (11%) | 2 (17%) | 0.535 |
| Chronic cough | 19 (20%) | 8 (67%) | 0.001 |

Data are expressed as *n* (%)

**Table 4** Outcomes of infants according to side of the hernia in those who had undergone FETO

| | Left CDH | Right CDH | *P* value |
|---|---|---|---|
| *n* | 91 | 15 | |
| Survival | 46 (51%) | 10 (67%) | 0.403 |
| Duration of ventilation (days) | 12 (3–22) | 16 (4–27) | 0.623 |
| HFOV | 48 (53%) | 8 (53%) | 1.000 |
| Nitric oxide | 37 (41%) | 4 (27%) | 0.504 |
| Time to full feeds (days) | 25 (22–31) | 26 (22–37) | 0.769 |
| Surgical repair of CDH | 61 (67%) | 11 (73%) | 0.771 |
| Time to surgery (days) | 5 (4–7) | 5 (4–6) | 0.981 |
| Patch repair | 47 (52%) | 8 (53%) | 0.714 |
| Post-operative mortality | 15 (16%) | 1 (7%) | 0.436 |
| Length of stay (days) | 30 (3–47) | 30 (5–46) | 0.704 |

Data are expressed as number (%) or median (interquartile range)

**Table 5** Long-term outcomes of infants according the to the side of the hernia in those who had undergone FETO

| | LCDH | RCDH | *P* value |
|---|---|---|---|
| *n* | 43 | 10 | |
| Hernia recurrence | 9 (21%) | 4 (40%) | 0.237 |
| Pectus deformity | 17 (40%) | 6 (60%) | 0.322 |
| Scoliosis | 5 (12%) | 3 (30%) | 0.174 |
| Fundoplication | 4 (9%) | 2 (20%) | 0.535 |
| Chronic cough | 14 (33%) | 7 (70%) | 0.326 |

Data are expressed as *n* (%)

with LCDH compared to 44% in infants with RCDH developed a recurrent hernia on average at the age of 4 months [16] and in the other study, the recurrence rates were 0.6% versus 4.1% [15]. Analysis of a multi-centre, multinational database of the results of 3,745 CDH infants born between 2007 and 2015 demonstrated that the higher proportion of large defects in right sided CDH accounted for the poorer survival in RCDH infants [17].

Several studies have described an increase in chest wall deformities following CDH repair [18–20]. In addition, there is evidence that the more severe diaphragmatic defects are associated with a significantly greater risk of pectus deformities [21]. In our series, overall more RCDH infants had musculoskeletal abnormalities at follow up. The RCDH infants were also more likely to suffer respiratory morbidity at follow up, as diagnosed by chronic cough or recurrent respiratory admissions.

Fifty-five percent of our RCDH infants survived which was similar to the survival rate of LCDH infants and similar survival rate to other centres with a high antenatal detection rate [4]. The survival rate is higher in centres where the majority of the RCDH cases had delayed presentation [6]. Our high antenatal detection for RCDH is higher than most published data [4, 6, 8, 22], but comparable to some [23]. The low antenatal detection rate of RCDH in some studies has been attributed to technical problems relating to echogenicity of the liver [23]. In a retrospective analysis of 22 RCDH, MRI was found to be useful in determination of liver position [23]. In a multicenter study of 178 infants, the 32 with RCDH were not more likely to have a patch repair, fundoplication or recurrence, but their post-operative mortality was higher and correlated with prenatal diagnosis and patch repair [24]. In our series the postoperative mortality was similar and the majority of both left and right CDH infants requiring a patch repair. In another study [25] infants with RCDH were more likely to require a patch repair, but with no significant difference in post-operative mortality, however, only 49 cases in total were included in that report. Our results that the mortality does not differ between R and LCDH infants is supported by a large multicenter multinational study of 3754 cases of CDH, where mortality was not associated with the side of the defect, but rather the size of the defect [17]. In a cohort of 24 patients O/E LHR, O/E total lung volume, percentage of herniated liver and postnatal use of ECMO were not prognostic indicators of survival in infants with RCDH and cut off values for LCDH infants did not extrapolate for RCDH infants. The authors suggested that L and RCHD behave differently [26]. Interestingly, when we considered only infants who had undergone FETO, there were no significant differences in either short (Table 4) or long (Table 5) outcomes according to side of defect. Those results might suggest that FETO may reduce the greater disadvantageous effects in utero that occur due to a right compared to a left sided hernia.

A retrospective review over a 12-year period of 330 CDH infants demonstrated that the 56 right sided cases had an increased duration of nitric oxide, were more likely to require a tracheostomy, were more likely to require supplemental oxygen on NICU discharge and have pulmonary hypertension requiring long term sildenafil therapy [27]. As in our study, despite the increased morbidity, the mortality was not higher in the right sided CDH infants. In another series, right sided CDH infants were more likely to require ECMO [28]. We found overall a greater need for iNO in infants with a right sided CDH, those results and other findings [27, 28] suggest such infants are more likely to suffer from pulmonary hypertension.

This study has strengths and some limitations. We report a consecutive series of CDH infants. The infants underwent management in a single centre with a standardized protocol [14], therefore, minimizing the effects of variations in treatment strategies over time. A limitation was the retrospective design, but we were able collect detailed follow-up information on 94.6% of the survivors.

## Conclusion

In conclusion, overall RCDH infants compared to infants with LCDH had greater morbidity at follow-up, but similar mortality. In infants, however, who had undergone FETO, there were no significant differences according to the side of defect in either mortality or short or longer term outcomes. Our results then are important for counselling parents and planning follow-up for such patients.

**Author contributions** KA and AG designed the study. KA, SAK, EEW and KT collected the data. KA, TD, KA and AG undertook the analysis. All authors were involved in the production of the first draft of the manuscript and approved the final version.

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### Compliance with ethical standards

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

**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** The 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.

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