**BMFMS Interim Grant Report.  Elspeth Whitby**

**The Prognostic value of consecutive MRI based lung measurements in CDH.**

Congenital diaphragmatic hernia occurs due to simple anatomical defect in the diaphragm that leads to herniation of abdominal viscera to the chest compressing the developing pulmonary and vascular structures. If this compression occurs at the canalicular stage, the period (before 26 weeks) at which bronchial and pulmonary vessels develop this leads to devastating physiological and pathological consequences. CDH is associated with wide range of morbidity and mortality rate 50-70% in isolated lesion. Early accurate information particularly in severe cases, would allow for early-informed decisions to be taken by parents especially if termination of pregnancy (TOP) is being considered.

A clear understanding of the longitudinal lung development in fetuses with congenital diaphragmatic hernia (CDH), and the impact of this on fetal survival have not yet been achieved. CDH is associated with pulmonary hypoplasia and pulmonary hypertension. In the isolated CDH Fetal lung volume is the primary indicator of pulmonary hypoplasia, survival and the subsequent long-term complications. Several attempts have been made to identify accurate antenatal variables that predict fetal outcomes. Fetal imaging facilitated quantification of fetal lung volume, which is essential for advising the management plan.

In addition we have noticed from follow up of cases which have had a MRI scan for congenital diaphragmatic hernia (CDH) that in the cases where 2 scans have been performed and there has been a reduction in the observed to expected lung volume that although these cases are well enough to undergo surgery they have died unexpectedly within a few days of seemingly successful surgery.

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MRI based serial total lung volume (TLV) assessments in foetuses with CDH may be useful to evaluate the individual lung development, and to ascertain the optimal gestational age for fetal lung evaluation to predict the clinical outcome.

**Hypothesis and objective**

**Hypothesis:** MRI assessment of fetal lungs at 20-24 weeks gestation provides a more accurate measurement of pulmonary hypoplasia than third trimester MRI when used to predict fetal survival.

**Secondary hypotheisis**: a significant change in the lung volume compared to expected indicates poor outcome.

**Objective:** To assess the value of 2 fetal lung measurements based on MRI scans as a prognostic factor for outcome.

**Study design and population**

Patients had a 20 US scan; cases with CDH were referred to FMU, cases considering continuation of the pregnancy referred to MRI. Cases continuing with the pregnancy and with over 40% expected lung volume at the time of diagnosis were recruited into the study and a follow up MRI scan performed at 32 weeks gestational age. (the majority of cases with less than 40% expected lung volume at the time of diagnosis are not well enough to undergo surgery and often die in the neonatal period).

A total of 18 cases are included in this report, Data is still pending for 2 cases**.**

**Data collection**

Information regarding the following variables was collected for data analysis: maternal age; gestational age at the two MRI examinations; gestational age and weight at birth; survival rate up to the date of discharge after surgery; birth weight; gender; side of hernia and position of liver.

**MRI fetal lung volume measurements**

The degree of fetal lung hypoplasia was assessed by obtaining the total lung volume (TLV), observed over expected (O/E) TLV and weekly lung growth rate.

Weekly growth rate= (subsequent TLV-initial TLV)/ (number of week between the 2 MR examinations).

Relative weekly growth rate = mean weekly growth rate of each CDH fetus/weekly growth rate of normal fetuses for the matched gestation)×100

## Results
### Demographics

A total of 18 fetuses with CDH were included in this analysis (9 male, 9 female) with 9 survived and 9 died (2 intrauterine fetal deaths at 32 weeks gestation; 5 died 12 hours post delivery; and 2 died 24 hours after surgery).

With regard to the following demographic variables: maternal age; gestational age at the first MRI [GA at 1st MRI] (weeks); gestational age at the second MRI [GA at 2nd MRI] (weeks); gestational age at birth (weeks); weight at birth (grams); and percentage of fetuses with right side and left side hernia in both survival and non-survival groups; as well as the percentage of fetuses with liver located in chest in both groups and the average of the time period between the two MRI.  There were no significant differences in all the above-mentioned parameters, between the survival and non-survival groups (p>0.05).

### Prognostic value of repeated MRI measurements
### Total lung volume

TLV at the early and late MRI assessments were significantly lower (P<0.001) than that of the expected value of healthy fetuses calculated by the equation presented by Rypens et al (1.) and when compared to our in house data. Although TLV in all but 1 CDH cases  increased with gestation as it would be expected, this increase was less than the increase in volume that for healthy fetuses at matched gestation (P<0.001).

**O/E TLV**

Unlike TLV, the individual O/E TLV varied during pregnancy. It increased in 6 of 18 fetuses and decreased in 12 of 18 fetuses.

2 of the six with increased O/E TLV and 7 out of the 12 with decreased O/E TLV survived. One fetus showed almost no change in TLV between the two MRI scans, and had the lowest O/E TLV on both scans and died 12 hours after birth.

**Weekly growth rate**

All CDH fetuses showed significantly less weekly growth rate than that of the of healthy fetuses (P<0.001). The deceased fetuses had a significantly lower weekly growth rate than those who survived (P<0.05). On average, the weekly growth rate of CDH fetuses was 37% of that of the normal fetuses at the matched gestation.

MRI tested variables in survivors and non-survivors of CDH

| Characteristics | Survivors | Non-survivors | P value* | AUC |
|---|---|---|---|---|
| First TLV | 8.96±176 | 5.45±1.05 | 0.003 | 1.00 |
| Last TLV | 21.5±6.92 | 11.94±5.73 | 0.02 | 0.82 |
| First O/E TLV% | 53±10 | 32±9 | 0.003 | 0.96 |
| Last O/E TLV | 46±9 | 29±15 | 0.021 | 0.82 |
| Difference in TLV in the interval between 2 MRI | 12.54 ±6.06 | 6.49±4.72 | 0.06 | N/A |
| Growth rate (ml/week) | 1.18±0.44 | 0.66±0.45 | 0.046 | 0.82 |

*Non-parametric student's T test, the results are expressed as Mean ±SEM

**Discussion**

The difference in volume between the early and late measurements was not significant between survived and non-survived foetuses (P=0.06).

There is significant difference in calculated means in early and late TLV and in the O/E TLV between the survived and died group in this cohort.

Early lung volume seems to predict fetal survival and correlates to the initial lung development stage just before the negative impact by the herniated organs start. In this study all early MRI scans conducted before 24 weeks gestation, At this stage fetal lung tissue is growing more than functioning.

These results are in agreement with the observations of from the FETO group where they observed that foetuses that received fetal endoluminal tracheal occlusion (FETO) in the period of 25-29 weeks gestation had obtained better lung growth and better lung morphology, (and consequently improved survival rate. Whereas no changes in the relative lung volume were observed in foetuses that received balloon insertion after 29 weeks gestation (2).

The early MRI scan informing the practice of how much of the lungs have already developed before the hernia and consequently how much chance that fetus has to survive.

However the results here disagree with previously reported results, which concluded that the late in gestation MRI examination of the fetal lung has more significant predictive capacity of fetal survival than the early in gestation MRI examination however there early scan was later than ours ( 26 weeks rather than 20weeks) and a wider age range at each scan time point (3,4).

This study not only evaluated the value of repeated scans to predict survival, it also standardized the timing of MRI examination and emphasized the predictive capacity of early MRI scans in CDH for fetal survival. However,

second MRI scans late in gestation before delivery might be useful for surgical preparation and to predict the long-term complication as well as agreeing delivery time and place, but this needs to be investigated to avoid un-necessary cost.

**Conclusion**

Results in the current observations confirm the suggestion that in fetuses with CDH the individual lung development is variable. The first MRI at the early gestational age (<24 weeks) seems to be more reliable to predict fetal survival than that conducted later in gestation (>30 weeks). Although there was significant difference in weekly growth rate between surviving  and non-surviving fetuses with CDH, its ability to predict fetal outcome was not significant. All the previous evidence might indicate that the fetal respiratory outcome is more directly related to the initial lung development than the change in lung development later in gestation. However these findings require a larger sample size to be confirmed.

**Hypothesis:** MRI assessment of fetal lungs at 20-24 weeks gestation provides a more accurate measurement of pulmonary hypoplasia than third trimester MRI when used to predict fetal survival.- proven.

**Secondary hypotheisis**: a significant change in the lung volume compared to expected indicates poor outcome.  Not proven.

**Future work:**

The data provided by this small study will be used to apply for larger grants to confirm the results of the hypothesis and look further into the secondary hypothesis.

**References**

1.      Rypens F, Metens T, Rocourt N, Sonigo P, Brunelle F, Quere MP, et al. Fetal lung volume: estimation at MR imaging-initial results. Radiology. 2001 Apr;219(1):236-41. PubMed PMID: 11274563.

2.      Cannie MM, Jani JC, De Keyzer F, Allegaert K, Dymarkowski S, Deprest J. Evidence and patterns in lung response after fetal tracheal occlusion: clinical controlled study. Radiology. 2009 Aug;252(2):526-33. PubMed PMID: 19508989.

3.      Coleman A, Phithakwatchara N, Shaaban A, Keswani S, Kline-Fath B, Kingma P, et al. Fetal lung growth represented by longitudinal changes in MRI-derived fetal lung volume parameters predicts survival in isolated left-sided congenital diaphragmatic hernia. Prenatal diagnosis. 2015 Feb;35(2):160-6. PubMed PMID: 25297802.

4.      Hagelstein C, Weidner M, Kilian AK, Debus A, Walleyo A, Schoenberg SO, et al. Repetitive MR measurements of lung volume in fetuses with congenital diaphragmatic hernia: individual development of pulmonary hypoplasia during pregnancy and calculation of weekly lung growth rates. European radiology. 2014 Feb;24(2):312-9. PubMed PMID: 24096317.