EDITORIAL ON:

The Challenge of Determining True Outcome of Congenital Diaphragmatic Hernia

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Congenital diaphragmatic hernia (CDH) remains one of the most challenging conditions to manage in neonatology and neonatal surgery. Despite significant advances in antenatal detection, antenatal therapy, neonatal intensive care and neonatal surgery, there is a significant mortality rate due to the combination of pulmonary hypoplasia, cardiac dysfunction and pulmonary hypertension. One of the major deficiencies in the literature has been a lack of high quality, multicentre data with a complete population denominator to accurately reflect the prognosis of this condition. Such studies would aid parental counselling, guide therapy and provide benchmarking for clinicians and centres. The paper by Long *et al* (ref 1) is a valuable contribution to the current evidence base, but we must be cautious in interpreting the presented data as true population outcomes.

The paper is a prospective study of a cohort of infants who presented to Paediatric Surgical Units in the UK and Ireland with diaphragmatic defects over an 18 month period during 2009-2010. The authors used robust methodology of case ascertainment, supported by the National Perinatal Epidemiology Unit, where local clinicians returned cards on a monthly basis. The data describe 219 live-born infants with an antenatal detection rate of 61%. This reflects 134 antenatally diagnosed CDH cases in 18 months. For the first 12 months of this study, the UK Obstetric Surveillance System (UKOSS) was conducting a study for pregnancies affected by CDH. Although these data have not yet been published, they identified 179 pregnancies in this period (https://www.npeu.ox.ac.uk/research/ukoss-cdh-174). Before discussing the outcome of postnatal surgical management, we should question why only approximately 50% of antenatally diagnosed cases have presented to surgical units postnatally to be included in the presented paper. Possible explanations include terminations of pregnancy and antenatally diagnosed newborns not reaching surgical centres.

Modern management of CDH starts from diagnosis. In the UK, universal fetal anomaly screening means antenatal diagnosis should now be achieved in over 75% cases. Antenatal diagnosis starts the process of assessment of likely outcome by measuring lung size and liver position and by searching for associated major anomalies that are known to impact negatively on outcome. Multidisciplinary counselling involves informing the expectant parents of the condition, together with the risks and available treatment options as well as the short term prognosis and long term issues. In the cohort reported by Long *et al*, only 78% expectant parents received counselling by a surgeon. Assuming some families in the UKOSS study opted for termination after diagnosis, it would be interesting to know what information was provided to them and by whom. Although no other antenatal interventions or severity markers are reported in the study, there is some evidence that antenatal diagnosis may have influenced the location of delivery, with only 25% of those diagnosed antenatally requiring postnatal transfer to the hospital where definitive surgical treatment took place. This is a lower number than one might expect and hints at an unseen cohort of neonates who were deemed too unstable for transfer to a surgical centre.

CDH repair was undertaken in 83% and 16% died without surgery. Those presenting post-natally were less compromised, as evidenced by the lower rate of high frequency ventilation, inotropic support, use of pulmonary vasodilators, and a higher chance of primary repair (suggesting smaller

defects). Only 75% post-natally diagnosed CDH were ventilated pre-surgery. No data are presented on age at diagnosis, time to presentation to paediatric surgical unit, or age at surgery. Some could be late (>24 hours) presenters by the definition of study entry. Echocardiography was carried out in 85% patients although the timing of the examination and findings are not presented. Treatment of pulmonary hypertension (mostly iNO) was employed in 36% of the cohort and in only 48% antenatally diagnosed CDH which is less than the International CDH Study group registry data. (ref 2) ECMO was only used in 4% which is also significantly lower than the registry. (ref 3) At the time of the study, ECMO was offered for CDH in 4 centres in the UK & Ireland. Two of these centres are not co-located with paediatric surgery units so some CDH patients treated in these ECMO units may not have been identified using the methodology.

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The authors identify some deviations from evidence-based practice. Surfactant was used in 25% despite being shown to be non-beneficial and possibly harmful. The authors also comment on other variations in practice although the data to support this are not presented. As expected, multivariable analysis showed that prenatal diagnosis, use of inotropes and pulmonary vasodilators were markers for death pre-surgery. Interestingly, associated anomalies did not predict mortality in this study though it is difficult to determine what percentage of associated anomalies were major (cardiac & chromosomal). Surprisingly, female sex was also a risk factor. This paper does demonstrate that the results of surgery for diaphragmatic defects in infants presenting to Paediatric Surgical Units in the UK and Ireland is excellent. There was a 98% 30 day post-operative survival rate (178/182). A 16% no repair rate is similar to that reported in other studies and the International CDH Study Group registry.

A similar "population based" contemporaneous study from France was published with data from 26 of the 34 centres that managed CDH during 2011. (ref 4) Unlike the UK & Ireland study, this used an online database (The French National CDH Registry) and included antenatal parameters and outcomes to 1 year. This study measured fetal risk indicators and reported on loss including terminations (11%). A higher proportion (87%) were antenatally diagnosed than in the UK & Ireland study. Mortality for antenatally diagnosed CDH was 39%, increasing to 47% when fetal loss and terminations were included. Mortality in isolated CDH was 34%, increased to 61% when CDH was associated with at least one other anomaly. There was a similarly low use of ECMO (6%). There was an attempt to determine defect size at surgery as per the International CDH Study Group grading (A-D). However, of the 114 newborns undergoing surgery, only 66 (58%) had this recorded. The value of this stratification is demonstrated in the difference in survival between groups with 97% survival for the A/B defects and only 60% survived in the C/D group. These data reflect the experience of the International CDH Study Group (ref 3) and may reflect a less selective cohort of CDH cases than in the UK & Ireland study. A similar proportion of patients survived to undergo surgical repair (82%), but there was a higher mortality following surgery. The reasons for the higher mortality after surgery in France are not clear but it does raise the possibility that paediatric surgical units in the UK and Ireland are treating less severe CDH cases.

In December 2014 the MBRRACE-UK Perinatal Confidential Enquiry into CDH was published with its key findings and recommendations. (ref 5) This study looked at a selection of patients in this BAPS-CASS study, in addition to antenatally diagnosed cases identified in the UKOSS study. Panels of experts reviewed the anonymised case notes of 57 patients and found significant variations in practice throughout the UK, including lack of consistency in information provided antenatally and

postnatally. Efforts have been made internationally to standardise management of CDH. The CDH EURO Consortium have published a 2015 update on standardising postnatal management of CDH (ref 6) and is presently updating advice on management of pulmonary hypertension in CDH. The Canadian Congenital Diaphragmatic Hernia Collaborative have this year published clinical practice guidelines for managing CDH, with key recommendations, strength of recommendation and level of evidence for each recommendation. (ref 7) It is hoped that implementation of the recommendations of MBRRACE will result in more standardised management of CDH in the UK and Ireland.

The difference in the results between the French and UK papers emphasises the potential weakness of publishing data on CDH survival without grading the severity of the disease and including a comprehensive and clearly defined denominator. The only way of uncovering the "hidden CDH mortality" is to introduce a National CDH Registry in the UK. A Registry would collect data from antenatal diagnosis and follow each case through to termination, death or long term follow-up. This will require full engagement across all specialties involved in diagnosing and managing CDH. Prospective case reporting and data collection would be the optimal way to ensure a complete denominator but it would also be useful to cross-reference against other established congenital anomaly registers such as the National Congenital Anomaly and Rare Disease Registration Service in England. Such a development is long overdue in the United Kingdom.

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