

Opinion

Fetal surgery for severe congenital diaphragmatic hernia?

Some fetal abnormalities, such as abdominal wall defects, are amenable to postnatal surgical correction with good results¹. In other conditions, however, the survival rate after postnatal surgery is relatively poor. In congenital diaphragmatic hernia (CDH), for example, this is because intrathoracic herniation of the abdominal viscera compromises the development of the fetal lungs, this being essentially the underlying mechanism for postnatal death^{2–6}.

The main objective of intrauterine surgery is to minimize abnormal development of vital organs rather than correction of an anatomical defect. The most extensively investigated fetal condition in the context of intrauterine surgery is CDH. Animal studies demonstrated that chronic intrauterine compression of the lungs due to CDH results in pulmonary hypoplasia and hypertension, and the severity of these conditions is substantially reduced by intrauterine correction^{7,8}. Encouraged by these results, Harrison *et al.* performed open fetal surgery for the correction of CDH in human fetuses⁹. However, the invasive nature of the intervention and the associated risks to maternal and fetal life and health resulted in abandonment of this technique. Based on the observation that in congenital laryngeal obstruction there is massive overgrowth of the fetal lungs, it was soon realized that tracheal occlusion could be an alternative to intrauterine surgical correction of the primary defect^{10,11}. In fetal life, the lungs produce fluid that escapes through the trachea and mouth into the amniotic cavity. Tracheal occlusion and consequent retention of the fluid within the lungs has been shown to improve pulmonary development^{12,13}.

A minimal access fetoscopic technique has been developed for tracheal occlusion which involves insertion of a balloon into the fetal trachea¹⁴. In the last decade, extensive experience in essentially three collaborating European centers has established the criteria for fetal endoscopic tracheal occlusion (FETO) and perfected the instrumentation and timing for both insertion and removal of the balloon¹⁵. Intrauterine surgery is undertaken in cases in which the condition is thought to be severe, with a high risk of postnatal death. Poor prognostic signs, used as criteria for requiring FETO, are intrathoracic herniation of the liver and low (<1) lung area-to-head circumference ratio (LHR)^{16,17}. Data from a multicenter study involving expectantly managed fetuses demonstrated that there was an inverse linear relationship between LHR, corrected for gestational age, and the likelihood of postnatal death due to pulmonary hypoplasia and/or hypertension⁴. Insertion of the balloon

should be as early in the pregnancy as possible to maximize the benefit on lung development. However, there is some evidence that if this is carried out before 26 weeks' gestation, there may be increased risk of tracheal damage^{18–20}. It is therefore felt best to insert the balloon at 26–28 weeks. The aim is for the trachea to remain occluded for as long as possible, but at the same time to remove it before birth, thereby avoiding the risk of immediate neonatal death. As a consequence of fetoscopic intervention, as well as of the association of CDH with polyhydramnios, there is a higher risk of premature delivery and it is therefore best that elective removal of the balloon occurs at around 34 weeks.

Combining the data from the three centers collaborating under the Eurofoetus consortium, FETO was carried out in 210 cases at a median gestational age of 27 weeks¹⁵. The CDH was left-sided in 84% of these cases and right-sided in 16%. Delivery was at a median age of 35 weeks and in total 98 (47%) babies were discharged from the hospital alive. On the basis of the relationship between survival and LHR corrected for gestational age in expectantly managed fetuses with CDH, it was estimated that FETO improved the survival rate from the expected 20% to 47%. The apparent better outcome of fetuses treated by FETO between 2000 and 2010, compared with historical controls managed expectantly between 1995 and 2004, could have been a mere consequence of selection bias or improvement of outcome with time. It was therefore considered necessary to investigate the potential benefit of FETO in an ongoing randomized study (NCT01240057).

In this issue of the Journal, Ruano *et al.*, report the results of a randomized clinical trial (RCT) of FETO versus postnatal management in severe CDH, conducted between May 2008 and July 2010 in a single center in Brazil²¹. Cases of isolated CDH with intrathoracic herniation of the liver and LHR <1 either underwent FETO at 26–30 weeks or were managed expectantly. The CDH was left-sided in 71% of cases and right-sided in 29%. In the 19 cases treated by FETO, delivery was at a median age of 35.4 weeks and the overall survival rate at 6 months of age was 52.6%. There were no technical problems in the introduction or removal of the balloon in any of the cases and the balloon remained inflated throughout intrauterine life in all fetuses. In the 19 cases managed expectantly, the median gestational age at delivery was 37.5 weeks and the survival rate was 5.3%. This 10-fold improvement in survival in a trial apparently conducted perfectly provides overwhelming evidence in favor of FETO.

The results of this RCT were remarkably similar to those of another study conducted by the same authors in the same center between January 2006 and December 2008²². In this case-control study, the methodology and results were reported as in a randomized study but the method of allocation of the patients into the two arms was not provided²². The CDH was left-sided in 69% of the cases and right-sided in 31%. In the 17 cases treated by FETO, delivery was at a median age of 35.6 weeks and the survival rate at 28 days was 52.9%. In the 18 cases managed expectantly, the median gestational age at delivery was 37.5 weeks and the survival rate was 5.6%. These results are particularly interesting because in one of the 17 cases in the FETO group it was not possible to insert the balloon inside the fetal trachea and in 10 of the 16 cases with successful FETO there was spontaneous deflation of the balloon within 5–6 weeks of insertion.

The survival rates of the FETO groups in the two studies by Ruano *et al.*^{21,22} were similar, and slightly higher than those of the cases treated by the Eurofoetus consortium (53% vs 47%)¹⁵, despite the higher incidence in the former of right-sided lesions, which are known to carry a worse prognosis. However, the most striking difference between the studies was in the survival rates of the expectantly managed groups, which was only 5% in the studies of Ruano *et al.*^{21,22}, compared with the estimated 20% in the study by the Eurofoetus consortium¹⁵.

The results of the Brazilian study²¹ contradict those of a previous randomized study of 24 cases with CDH conducted in the USA²³. The survival rate in the fetuses treated with tracheal occlusion was not significantly different from that in the fetuses managed expectantly (73% vs. 77%). The high survival in both arms of the study may reflect a lower severity of the disease because the required LHR was < 1.42³, rather than < 1 as used by Ruano *et al.*²¹.

It is essential that, before FETO is offered routinely in cases of severe CDH, the ongoing Eurofoetus randomized study is completed. This is being carried out in several leading European and North American centers of fetal medicine, where the survival rate of cases with severe CDH following FETO is lower, and the rate in those managed expectantly is considerably higher than the rates reported in the Brazilian study²¹. In the meantime, FETO should not be recommended outside centers with considerable experience in FETO and it should preferably be undertaken only within the confines of the ongoing multicenter randomized study.

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