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Letter to the Editor

Prenatal Therapies in Congenital Diaphragmatic Hernia, Where we are Now

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DEAR EDITOR,

Congenital diaphragmatic hernia (CDH) is a discontinuity of the diaphragm, and this allows abdominal viscera to herniate into the chest. This condition is associated with a high neonatal morbidity and mortality, secondary to severe pulmonary hypoplasia and pulmonary hypertension [1]. Although the results have improved in the last years, based in prenatal diagnosis, prognostic markers, prenatal intervention by fetal endoscopic tracheal occlusion (FETO) and post natal care as refer an experienced tertiary center with a high case volume (minimum 6 by year), protocol established of hemodinamical and respiratory variables, and rescue therapy as high-frequency oscillatory ventilation, inhaled nitric oxide and extracorporeal membrane oxygenation (ECMO) [2]. The origin of the problem is in early stages of pregnancy, and possibly, this may be the best stage for intervention. The unique therapy prenatal approved (FETO), is not free of the adverse effect, mainly a significant risk for prematurity and all its consequences. On the other hand, a group of neonates die from severe pulmonary hypoplasia, despite intervention [3]. For this reason, other therapeutical alternatives should be raised in those neonates with poor prognostic factors. This new approach, must be minimally invasive that avoided complications as premature birth. The first point to check will be if the hypoplasia pulmonary is by mass effect or other factors are responsible of the pulmonary hypertension severity at birth and the cause of death. Derderian S et al, assessed whether the lesions in which a space-occupying mass in the chest may contribute of the same way for developing of severe pulmonary hypoplasia. They determined that patients with severe CDH have pulmonary hypoplasia associated to increased pulmonary vascular resistance more than other diseases in which a space-occupying mass in the chest. Supporting the hypothesis that the vascular compromise is a important component in the development of pulmonary hypertension and not simply by the effect of mass in the chest. This research assesses that anatomic factors and physiologic factors such as inflammatory mediators are responsible of the vascular compromise, which could lead to severe hypoxemia in some patients [4]. CHD shows a disrupted pulmonary vascular development, associated to pulmonary arterial smooth muscle cell hyperplasia hyper contractility, the total size of the pulmonary vascular bed is reduced and the thickness of the adventitia and media of the pulmonary arteries is increased [5]. Hence, postnatal treatment may fail in some patients. By the above, exploring new prenatal therapeutic strategies to mitigate vascular remodeling, could be an alternative in this condition. This concept is reinforced by the latest report of Cochrane, who informed that there is insufficient evidence to recommend in-utero intervention for fetuses with severe CDH (FETO) as a part of routine clinical practice [6]. Some studies in animals, have demonstrated that pharmacology therapy can be an option to try reversing the vascular remodeling (hypertrophy of pulmonary arterioles). This research has been developed by modelling the induction of diaphragmatic hernia in rats with nitrofen and others using lambs [5,7,8,9]. The most used drugs have been sildenafil, steroid and vitamin A. Other alternatives have been explored, such as, the platelet derived growth factor (PDGF) receptor antagonist (imatinib) and a slow-release form of a novel synthetic prostacyclin agonist with thromboxane inhibitory activity [7,9] The studies showed variable results some therapies. Steroids, for instance, showed different clinical outcomes and even harmful results. Dexamethasone showed harmful effects as it decreases the number of arterioles and arteries and a significant increase in the percent of medial wall thickness. It was also associated with altered fetal and pulmonary growth. Benefits such as increased pulmonary compliance have been reported [5,10]. Moreover, in preterm delivery ≤34 week gestation antenatal steroids should be given, this may decrease morbidity resulting from preterm delivery. Another therapy evaluated, is vitamin A. CDH is a complex developmental defect that is etiologically heterogeneous and the cause is unknown. But, the involvement of retinol signaling pathway in the development of the diaphragm and low levels of vitamin A and retinol-binding protein have been found. It is suggests that alteration in the metabolism of vitamin A, may participate in the pathogenesis of the CHD. Vitamin A promotes airway branching, lung growth, differentiation of bronchial epithelial cells, and promotes septation of saccules and thinning of septal walls (alveolarization) [8,11]. Studies in animals, have demonstrated that the supply of vitamin A in antenatal form improvement in lung function and structural maturation. Vitamin A, accelerated the maturation of pulmonary, but the require doses is to be determined yet. [11]. Other studies have evaluated combined therapy, with tracheal occlusion and vitamin A, without additional benefits [12]. Due to the complexity of this condition, sildenafil is considered as a prenatal option. In animal models, prenatal neonatal treatment

with sildenafil improved lung structure, increased vessel density and decreased right ventricular hypertrophy while increasing pulmonary, however this has not been correlated with clinical outcomes. Probably because sildenafil increases in the number of arterioles only and not the number of arteries, neither in percentage of medial wall thickness [5,10]. Citrate silde nail appears to be a safe therapy during the pregnancy, and it is not is linked to adverse effects for neither the mother nor the fetus. Its's use in pregnancy has been limited to some maternal conditions as severe hypertension pulmonary, preeclampsia, among others [13]. It is appear to be an interesting therapy in cases with poor prognostic markers. These prognostic markers are well established such as liver herniation, sonographic measurement of contra lateral lung area-to-head ratio (LHR), there were no survivors with an LHR <0.6, whereas survival was 100 % if the LHR was >1.35. However, this parameter depends on gestational age. As LHR is a variable across gestational age, this can be corrected by measuring expected LHR-to-observed LHR (O/E LHR) ratio, and several studies have used this to predict mortality in fetuses with CDH. Other parameters that allow us to determine the severity of lung disease include measuring fetal lung volume (FLV) at 34 week gestation on fetal MRI [14]. Hence, in cases of fetal CDH with poor prognostics and high risk of death, antenatal therapy must be considered as an option to improve the final result.

As a conclusion, the assessment of new prenatal therapies should be considered as an option to explore in cases with poor vital prognosis. The only current prenatal therapy is not free of adverse effects (delivery preterm), and postnatal management in these cases, including ECMO, had serious sequelae, mainly neurological and pulmonary. In addition, a group of neonates are going to die in spite of extreme medical therapy.

Regards,

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