INTRODUCTION

Congenital diaphragmatic hernia (CDH) occurs in approximately 1 of 2500 newborn infants. The cause is unknown. There is failure of normal closure of the pleuroperitoneal canal in the developing embryo. Abdominal contents herniate and compress the ipsilateral developing lung, causing pulmonary hypoplasia and hypertension ***(Gosche et al., 2005).***

Although CDH is more likely manifested on the first days of life, there are some cases report late presenting congenital diaphragmatic hernias. There is little consensus in the age definition of late presenting CDH, although many authors have used between 1 and 2 months as the lower age limit ***(Mei-Zahav et al., 2003).***

Although the diagnosis of late-presenting CDH is usually easily made by chest radiograph, the symptoms preceding diagnosis can be different. Congenital diaphragmatic hernia study group retrospectively reviewed 79 cases of late-presenting CDH collected during 1995-2005. In these cases, presenting symptoms are respiratory in 43%, gastrointestinal in 33%, both in 13% and none in 11% ***(Kitano et al., 2005)***

CDH remains one of the most difficult problems of anesthesiology and neonatal surgery. Its mechanisms are beginning to be unveiled, but the severity of the lung and other lesions require the use of the entire armamentarium of sophisticated neonatal care. This, together with the rarity of the condition, make the setting of solid evidence-based protocols of management very difficult ***(Hartnett, 2008).***

The perspectives of fetal manipulation or even of prophylactic drug treatment remain still at an embryonal stage and, most probably, this condition will remain a hot topic of research in the coming years ***(Hartnett, 2008)***.

Although the management of infants with CDH remains a major challenge in anesthesiology and neonatology worldwide, most current therapeutic recommendations are based primarily on observational studies, historical data, and biologic plausibility derived from animal studies. There is a paucity of large randomized, controlled studies among infants with this condition ***(Tracy et al., 2010).***

Whereas in the absence of such trials it is impossible to make sound therapeutic recommendations, current evidence suggests that better outcomes might be achieved by delivering infants with CDH at experienced centers, by delaying surgical repair until an acceptable degree of hemodynamic and respiratory stability is established, and by the judicious utilization of nonaggressive mechanical ventilation and permissive hypercapnea. Other therapeutic modalities, such as high frequency oscillatory ventilation, inhaled nitric oxide, and extra-corporeal membrane oxygenation (ECMO), may provide additional advantages for selected infants. Only by establishing networks of centers in which enough infants with CDH are managed will we be able to conduct appropriately sized randomized trials that can contribute to answer some of the crucial dilemmas about the management of these infants and can shed light onto their long term outcome ***(Migliazza et al., 2007).***

Aim of the Work

The aim of this work is to show the new advances in anesthetic management of congenital diaphragmatic hernia repair.

EMBRYOLOGY

The transition from fetal to postnatal life requires dramatic adaptation in the physiology of respiration from complete dependency on the placenta to gas exchange via air-filled, perfused lungs within seconds after birth. For premature or asphyxiated infants or in the setting of anomalies associated with cardiorespiratory dysfunction (e.g., congenital diaphragmatic hernia, tracheoesophageal fistula, some types of congenital heart disease), the superimposed effects of surgery, inhalational anesthetics and other medications, positive pressure ventilation, and infection add to the critical short term challenge of maintaining physiologic stability while minimizing long-term morbidity ***(Joshi and Kotecha, 2007).***

The development of the pulmonary system has been divided into five stages (embryonic, pseudoglandular, canalicular, saccular, alveolar) based on morphology. Knowledge of the sequence of developmental events can inform estimates of the timing of congenital malformations associated with fetal-maternal factors (e.g.oligohydramnios), genetic factors, or developmental insult ***(Joshi and Kotecha, 2007).***

The embryonic stage (0–7 weeks gestational age)

At 3–4weeks gestational age, the laryngotracheal groove first appears as a ventral diverticulum from the primitive foregut, lined by epithelial cells of endodermal origin. During

the embryonic stage, the large airways first appear as epithelial cells from the foregut that eventually invade the mesenchyme to form the trachea. This structure then undergoes a series of branching events, requiring interaction of epithelial and mesenchymal cells. By the fifth week of gestation, the branching has advanced to the level of lobar and segmental bronchi, so that five pulmonary lobes have been formed. By the end of the embryonic stage, the 18 major lobules are easily recognized ***(Kotecha, 2005).***

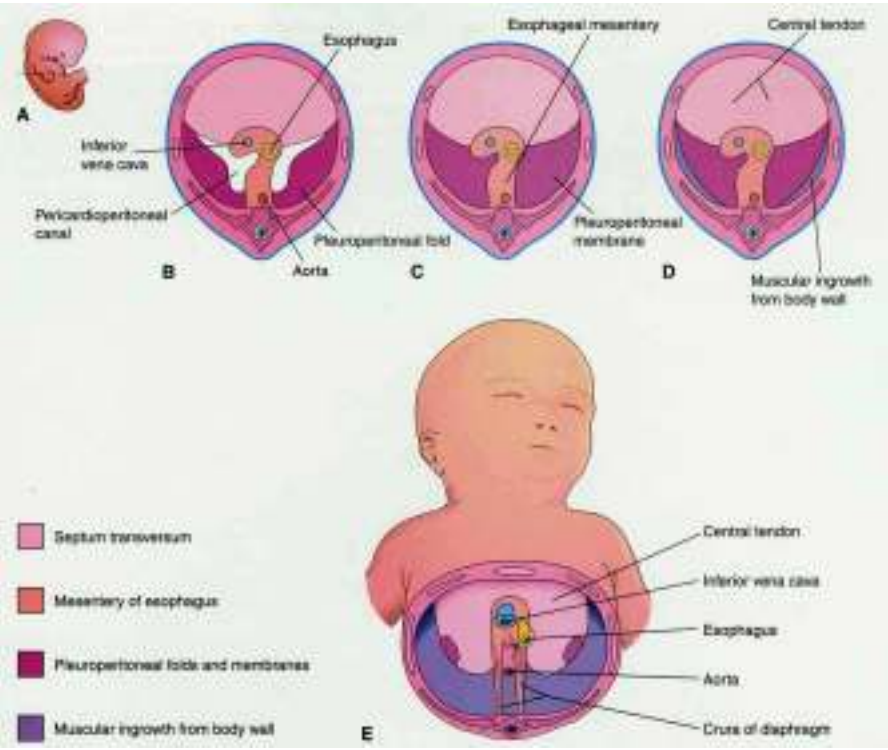

Figure (1): Formation of diaphragm ***(Larsen, 2001).***

Although the airway epithelium resembles that of the esophagus at this stage, over the course of development, differentiation and maturation of the primitive endodermal cells produce the population of epithelial cells that characterize the adult lung. During the embryonic stage, the pulmonary vasculature develops in parallel with the airways. At 4 weeks gestational age, endothelial cell precursors around the developing lung bud eventually form endothelial tubes that continuously coalesce to form the intrapulmonary arteries. Congenital malformations associated with events during the embryonic stage involve the large airways and/or whole sections of lung and include pulmonary agenesis, ectopic lobes, lobar cysts, agenesis, malformation, stenosis, or malacia and vascular malformations ***(Hislop and Pierce, 2003).***

Pseudoglandular stage (7–17 weeks gestational age)

The most rapid branching of the airways occurs during the pseudoglandular stage. As the epithelial cells divide, the surrounding mass of gland-like mesenchyme regulates the branching. The mesenchyme inhibits branching in the trachea but induces branching in bronchi. By 14 weeks gestational age, 70 % of the airways present at birth have formed, and by 17 weeks, the conducting airways, terminal bronchioles, and primitive acini are completely established. In parallel with the development of the airways during the pseudoglandular stage, the vascular structures branch rapidly leading to the formation

of the pulmonary arteries and veins, which, along with the airways are derived from mesenchymal tissue ***(Scott, 2007).***

Further differentiation of the pseudostratified epithelium of the airway involves its progressive replacement with columnar cells proximally and cuboidal cells distally. Between 11 and 16 weeks gestation, ciliated epithelium appears and airway mucus is first synthesized. The cuboidal cells eventually mature into type II pneumocytes. Insults during this stage of lung growth can alter bronchial growth patterns, producing lesions characterized by poor lung growth (pulmonary hypoplasia), sequestration lesions, and cystic adenomatoid malformations ***(Scott, 2007).***

During this critical period of lung growth, the muscul-otendinous, dome-shaped diaphragm develops, which, in addition to becoming the primary muscle of respiration, serves to separate the pleural and peritoneal cavities and promote pulmonary growth. At the end of the third week of gestation, the diaphragm consists of a collection of mesodermal tissue, the septum transversum, which separates the pleural-pericardial cavity from the peritoneal cavity. Of note, pleural-peritoneal canals allow limited but persistent communication between these two cavities. The septum transversum migrates downward from the level of the occipital and upper cervical somites (C3) to the level of the thoracic somites by the sixth week of gestation and to the level of L1 by the eighth week ***(Arkovitz et al., 2005).***

During the descent, the neural tissue of C3–C5 origin penetrates the mesoderm and eventually develops into the phrenic nerve. At approximately this time, the right and left pleuroperitoneal membranes close the communication between pleural and peritoneal cavities. Congenital diaphragmatic hernia (CDH) results from failure of complete separation of the pleural and peritoneal cavities. At 10–12 weeks gestation, before the bowel returns to the abdominal cavity from the amnion (where it resides in early gestation), closure of diaphragm is complete. If the separation of the two body cavities is incomplete, the bowel enters the chest, the path of least resistance. However, bowel then occupies space needed for lung growth ***(Arkovitz et al., 2005).***

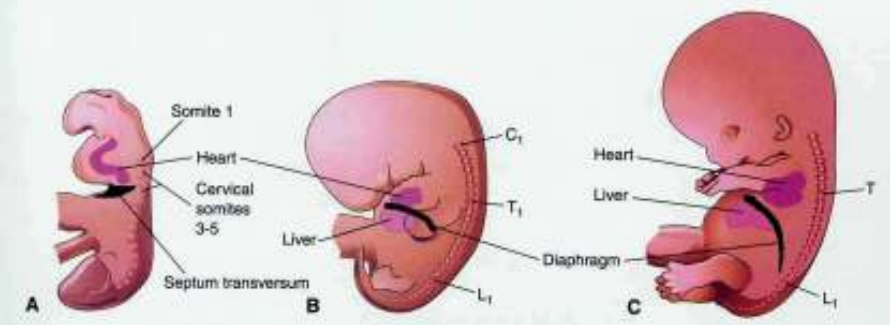

Figure (2): Descent of the diaphragm ***(Larsen, 2001)***.

A posterolateral CDH (Bochdalek hernia) results from failure of closure of the pleural-peritoneal membranes, accounts for 95 % of diaphragmatic hernias (approximately 1/2,000–1/4,000 live births), and is usually unilateral (78 % on left, 20 % on right, 2 % bilateral) but often is associated with significant ipsilateral pulmonary hypoplasia as well as abnormal

development of the contralateral lung. In addition to abnormal lung development, other anomalies not directly related to the hernia often accompany this lesion (e.g., congenital heart disease, central nervous system anomalies) ***(Arkovitz et al., 2005)***.

The etiology of CDH is not completely understood, but genetic associations have been noted. Intrauterine exposure to teratogens affecting the retinoic acid enzyme pathway induces CDH through malformation of the primordial non muscular diaphragmatic tissue as early as the fifth to seventh weeks of gestation via a cascade of events that leads to failure of closure of the posterolateral walls in later gestation. Of note, experiments in transgenic mice have induced absence of lung development without CDH, implying that CDH is a primary event ***(Arkovitz et al., 2005).***

Canalicular stage (17–27 weeks)

During the canalicular stage, the distal airways develop into primary acini, consisting of respiratory bronchioles, alveolar ducts, and rudimentary alveoli. The surrounding capillaries develop in parallel. These represent the first units of gas exchange. Epithelial cells differentiate into type I and II pneumocytes, with type I cells incorporated into the first alveolar- capillary barrier. Surfactant can be detected at approximately 24 weeks with active production beginning at 26–28 weeks. After 26 weeks gestation, respiratory saccules lie in close contact with pulmonary capillaries, increasing the likelihood of adequate gas exchange essential for extra uterine

viability. Before this developmental age, gas exchange may be compromised because of inadequate surface area and function of the lung parenchyma and/or vasculature. For example, survival after birth during the canalicular stage, in part, is determined by surfactant deficiency (respiratory distress syndrome) ***(Clugston and Greer, 2007).***

Saccular phase (28–36 weeks gestation)

An increase in the surface area of gas exchange is the major feature of the saccular phase of lung growth. The peripheral areas of the lung enlarge, as the acini dilate and the acinar walls thin. Gas exchange is further facilitated as type II pneumocytes increasingly differentiate into type I cells and capillaries develop in close approximation ***(Scott, 2007).***

Alveolar phase (36 weeks gestation until ~2–3 years)

During the alveolar phase, the surface area for gas exchange increases as alveoli septate and increase in number, a process that continues through the third year of life. Type II pneumocytes proliferate and become prominent after 34–36weeks of gestation.

The key feature of type II pneumocytes is eosinophilic lamellar bodies, specialized vesicles that store and release surfactant lipids and proteins at term, the total number of alveoli in the healthy infant is only 20–50 million, increasing to adult numbers of more than 300 million per lung, by 2–3 years of age ***(Whitsett et al., 2010).***

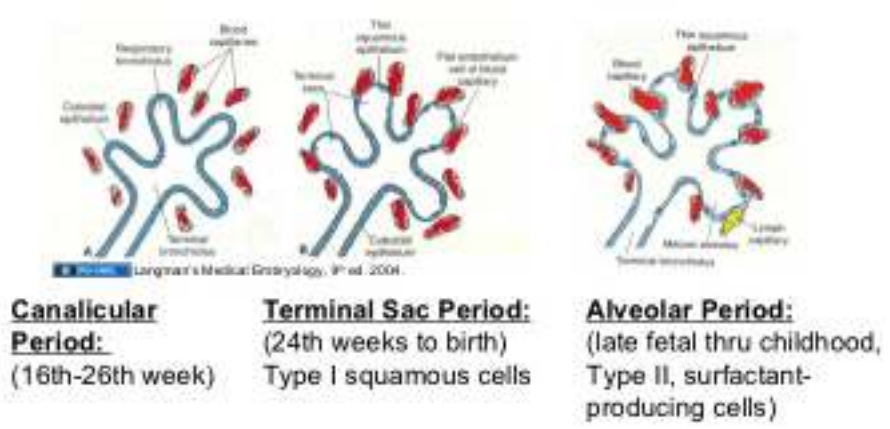

Figure (3): Development of lung tissue involved in air exchange ***(Nguyen and Senior, 2006).***

Developmental abnormalities during the alveolar phase can result in respiratory distress syndrome, chronic lung disease, and dysplasia of the acini or alveolar capillaries. Although rare, several genetic disorders can also adversely affect lung development, such as mutations in the surfactant protein system. The molecular basis of the control of lung development is incompletely understood, but involves many transcription and growth factors in critical roles. In addition, the surrounding mesenchyme appears to direct the developing epithelial cells, and the mesenchymal-epithelium interactions seem to be essential for normal development. A variety of mechanical factors affect lung growth in utero and postnatally. For example, in animal models, inadequate fetal lung fluid secondary to a deficiency of amniotic fluid can induce pulmonary hypoplasia ***(Whitsett et al., 2010).***

In humans, pulmonary hypoplasia is prominent in the oligohydramnios sequence ("Potter's syndrome") associated with low urine output secondary to renal dysgenesis. Similarly, oligohydramnios secondary to chronic leakage of amniotic fluid can interfere with lung development. Finally, the role of maintaining adequate lung volume with fluid in promoting lung growth and development during the canalicular and saccular stages is the basis of various fetal therapeutic interventions (e.g., in utero tracheal occlusion) intended to induce lung growth in the presence of CDH ***(Khan et al., 2007).***

Fetal breathing may contribute to maintaining sufficient lung volume and, therefore, growth of the lung, possibly by activating stretch-mediated release of growth factors. When fetal breathing is ablated in animals, lung growth decreases. Decreased fetal breathing movements may underlie the pulmonary hypoplasia associated with some neurologic disorders, abdominal wall defects, and in utero exposure to certain substances (e.g., chronic exposure todiazepam and possibly maternal smoking). Although lesions occupying the intra thoracic space (e.g., CDH, congenital cystic adenoid malformations) and skeletal defects involving the thorax can impede lung development secondary to obvious mechanical effects, these anomalies may also impair fetal breathing, which may exacerbate the primary effect of the space-occupying lesion ***(Khan et al., 2007).***

Postnatal development of the lung

Postnatal development of the lung includes the completion of the alveolar stage to achieve airway and micro vascular maturation (birth to 23 years). That is, alveolar capillary micro architecture is transformed from double to single capillary networks. Postnatal therapy with corticosteroids may impair lung growth by arresting this process. Beyond the first two years of life and until late adolescence, the lungs continue to grow via increase in size of both bronchioles and alveoli. Whether late alveolarization continues after the toddler years (and beyond), and by what mechanism, remains controversial ***(Van Marter, 2005).***

Premature birth and/or infection can severely impact growth of the lung, especially alveolarization, For example, in utero infection (e.g., chorioamnionitis) and markers of lung inflammation have been associated with an increased incidence of chronic lung disease characterized by poor lung development, In addition, the life saving supportive therapies (e.g., mechanical ventilation, supplemental oxygen) commonly delivered to the premature infant have been reported to impair normal lung development, resulting in abnormal alveolarization Specifically, oxidative stress has also been implicated in disorders of lung growth ***(Van Marter, 2005).***

ANATOMY OF THE DIAPHRAGM

The diaphragm is a musculo-fibrous sheet separating the thorax and the abdomen. It takes the shape of an elliptical cylindroid capped with a dome. The use of the word dome in itself introduces a degree of inaccuracy, as it gives the impression that there is a curved structure rising equally from the sides to a central point, whereas a more accurate description is of a pair of cupolas either side of a central plateau. This elliptical shape is determined by the thoracic outlet, which will also have an influence upon the function of the diaphragm, as it will determine the anatomical structure of it. This is because the thoracic outlet is set obliquely to the coronal plane, being superior anteriorly and inferior posteriorly ***(De Troyer et al., 2003).***

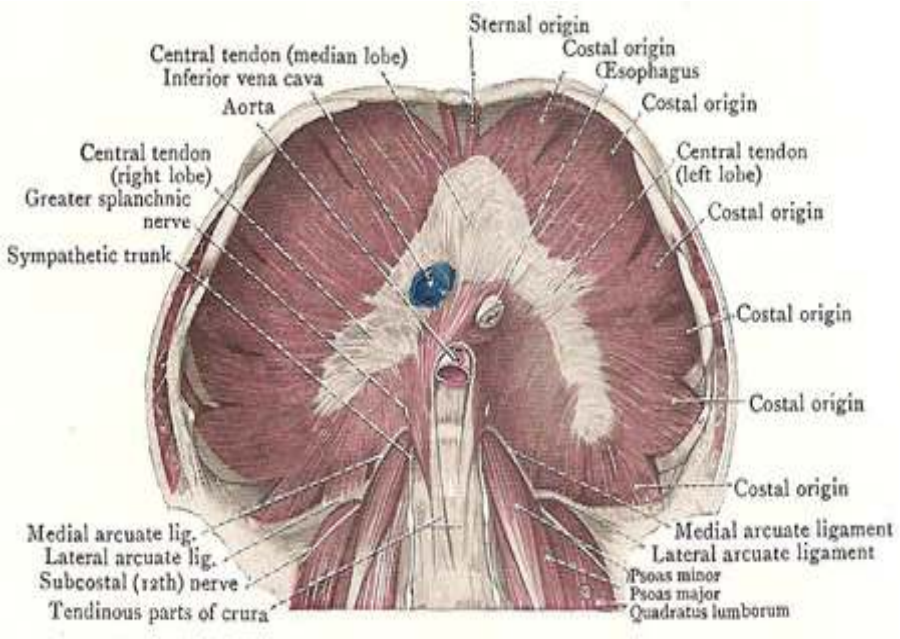

Figure (4): Anatomy of diaphragm shows sites of Bockdalek and Morgagni hernias ***(Eren and Ciriş, 2005).***

The skeletal attachments of the diaphragm to the thoracic outlet commence at the xiphoid process and symphysis centrally, and, moving laterally, the ventral ends and costal cartilages of the seventh to twelfth ribs, the transverse processes of the first lumbar vertebra, and the bodies and symphyses of the first three lumbar vertebrae. As the periphery of the diaphragm is attached to the thoracic outlet anteriorly and laterally, and beyond it posteriorly, it will follow that the anterior portion of the diaphragm will be shorter than the lateral and posterior parts ***(De Troyer et al., 2003).***

The presence of the viscera in the thorax and abdomen causes the part of the diaphragm separating them to be roughly horizontal, but will determine the shape of the unstressed dome. This may be considered as a separate zone from the other part of the diaphragm, and will be referred to as the diaphragmatic zone. The other part of the diaphragm will be referred to as the apposition zone, because it assumes a roughly vertical direction. It is also the area through which the rib cage is opposed to the abdominal contents and thus exposed to abdominal pressure ***(Muller et al., 2007).***

Diaphragmatic Attachments:

The sternal part is attached by two slips to the back of the xiphoid process, although these slips may be absent. The costal part is attached to the internal surfaces of the lower six costal cartilages and their adjoining ribs, the vertical fibers of the diaphragm interdigitating with the horizontal fibers from the