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Konjenital Diafragmatik Herni Tedavisinde Prenatal Dönemde Uygulanan Fetal Endoskopik Trakeal Oklüzyon İşleminin Etkinliği

Effectiveness Of Fetal Endoscopic Tracheal Occlusion Therapy In The Prenatal Period Of Congenital Diaphragmatic Hernia

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ÖZET

Konjenital diyafragmatik herni nadir görülen malformasyonlardan biridir (0.8-5/10000). Postnatal dönemde tedavi seçenekleri fazla olmasına rağmen, malformasyonun şiddeti arttıkça, tedaviye yanıt azaltmaktadır. Diafragmatik defektten geçen intraabdominal organların basısı ile akciğer gelişimde kısıtlanma mevcuttur. Akciğer dokusundaki hipoplaziye bağlı olarak ortaya çıkan pulmoner hipertansiyon şiddeti, postnatal dönemdeki morbidite ve mortalite ile yakından ilişkilidir. Akciğer dokusunun yanında, kalbe olan bası nedeniyle de özellikle sol ventrikül hipoplazisi de ortaya çıkabilmektedir. Tüm bu nedenlerden dolayı, daha prenatal dönemde, doku hipoplazisi gelişmeden önce tedavi seçenekleri araştırılmaya başlanmıştır. Son 20 yıllık dönemde, teknolojideki gelişmelere paralel olarak ultrason ve magnetik rezonans cihazlarında ciddi gelişmeler olmuştur. Buna bağlı olarak ta prenatal dönemde diyafragmatik hernisi olan fetuslerin akciğer gelişimleri daha iyi takip edilebilir olmuştur. Prenatal dönemde akciğer dokusunda ciddi azalmalar saptanan hastalara yönelik, doğum sonrası yaşam beklentisini arttrmak adına günümüzde tedavi seçeneği verebilen yegane yöntem, fetal endoskopik trakeal oklüzyondur. Bu işlem ile prenatal dönemde trakeaya yerleştirilen bir balon ile akciğerden salınan sıvıların akciğer içinde birikmesi amaçlanır. Bu biriken sıvılar nedeniyle, akciğer volümü genişler, doku hipoplazisi azalır, pulmoner hipertansiyon derecesi azalır. Fetal trakeal oklüzyon işlemi, yenidoğan sonuçlarında iyileşmeler sağlamış olsa da, işlemin uygulanma şekline bağlı olarak komplikasyon ihtimali de söz konusudur. Erken membran rüptürü, preterm eylem gibi değişik komplikasyonlar işleme bağlı olarak görülebilmektedir. Bu nedenden dolayı trakeal oklüzyon işlemi için aday olacak vakaları iyi seçmek, kar-zarar oranını iyi hesaplamak gerekmektedir. Bu çalışmamızda, fetal endoskopik trakeal oklüzyon işleminin uygulanmasında en son güncel yayınları inceledik. İşlemin hangi hastalara uygulanabileceğinin ve uygulandığı takdirde faydalarının ve zararlarının neler olabileceğini araştırdık.

Anahtar kelimeler: Konjenital diyafragmatik herni, fetal endoskopik trakeal oklüzyon, o/e LHR

ABSTRACT

Congenital diaphragmatic hernia is one of the rare malformations (0.8-5 / 10000). Although there are many treatment options in the postnatal period, as the severity of the malformation increases, the response to treatment decreases. Lung development is restricted by the compression of intraabdominal organs passing through the diaphragmatic defect. The severity of pulmonary hypertension due to hypoplasia in the lung tissue is closely related to postnatal morbidity and mortality. In addition to the lung tissue, left ventricular hypoplasia may also occur due to pressure on the heart. For all these reasons, treatment options have begun to be investigated even in the prenatal period, before tissue hypoplasia develops. In the last 20 years, there have been serious

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developments in ultrasound and magnetic resonance devices in parallel with the developments in technology. Accordingly, lung development of fetuses with diaphragmatic hernia during prenatal period has been better followed. Fetal endoscopic tracheal occlusion is the only method that can give treatment options to patients who are found to have severely decreased lung tissue in the prenatal period, in order to increase postpartum life expectancy. With this procedure, it is aimed to collect the fluids released from the lung with a balloon placed in the trachea in the prenatal period. Because of these accumulated fluids, the lung volume expands, tissue hypoplasia decreases, and the degree of pulmonary hypertension decreases. Although the fetal tracheal occlusion procedure has improved neonatal outcomes, there is a possibility of complications depending on the way the procedure is applied. Various complications such as premature rupture of membranes and preterm labor can be seen depending on the procedure. For this reason, it is necessary to choose the candidates for the tracheal occlusion procedure well and to calculate the profit-loss ratio well. In this study, current publications of fetal endoscopic tracheal occlusion procedure were reviewed. It was investigated on which patients the procedure could be applied and what the benefits and harms might be if it was applied.

Keywords: Congenital diaphragmatic hernia, fetal endoscopic tracheal occlusion, o/e LHR

Introduction:

Congenital diaphragmatic hernia (CDH) is a defect that occurs in the formation phase of the diaphragm. The developmental stage of the diaphragm in the embryological period develops between the 4th and 10th weeks of gestation [1]. The diaphragm formation defect that occurs in these weeks causes congenital diaphragmatic hernia. From this defect, organs in the abdominal region are herniated into the chest cavity. Although the incidence is stated at different rates in different publications, it is observed as approximately 0.8-5 / 10000 [2]. It results in pulmonary hypoplasia and pulmonary hypertension due to compression of herniated organs in the chest cavity. Most of the cases (70-90%) are caused by defects in the posterolateral region of the diaphragm. Hernias formed in this way are called Bochadelek hernias. The remaining cases are composed of hernias (10-15%) consisting of defects in the anterior region. Only 2% of the cases are hernias consisting of the central region.

CDH can be surgically repaired after birth. However, tissue hypoplasia in the lung tissue and pulmonary hypertension due to hyperplasia in the vascular wall, brings many problems in the postnatal period. Efforts to prevent these tissue damages with the interventions that can be done in the prenatal period have created intensive work areas in recent years. Especially fetal endoscopic tracheal occlusion therapy has increased its popularity in recent years. By applying fetal endoscopic tracheal occlusion, an increase in pulmonary volume and a decrease in pulmonary hypertension could be achieved. Of course, it has certain limitations and complications as it requires fetal invasive intervention. In this study, the effects of fetal endoscopic tracheal occlusion treatment in pregnant women with congenital diaphragmatic hernia will be evaluated in the light of the latest up-to-date information.

Embryology and Genetics:

The diaphragm develops from the pleroperitoneal folds and dorsal mesentery when the embryo is 9 mm [3]. Defects formed in the fusion of these structures cause the formation of diaphragmatic hernia. The formation of the diaphragm is completed in about the 9th week. Tissue passage occurs from the defect that cannot complete its integrity. Posterolateral hernias constitute the majority of cases (Bochadelek type hernia). If the defect is anteriorly, the defect is called Morgagni type hernia. Bilateral diaphragmatic hernias occur relatively rarely (2%), but the prognosis is worse in these cases [4].

Lung development also develops between the 10th and 14th weeks. Since the development defect in the diaphragm occurs before the lung starts to develop, herniation of the abdominal organs occurs when the lung is not yet developed. Due to compression of the intestines and other organs in the thoracic cavity, it causes decreased bronchiolar branching in the pulmonary tissue, decreased surfactant production and consequently pulmonary hypertension [5].

Although congenital diaphragmatic hernias are generally seen sporadically, there is a genetic origin in approximately 10-30% of the cases [6]. Coexisting syndromes are shown in table-1 [7]. Invasive karyotyping should be performed in all patients with congenital diaphragmatic hernia. Even if there is no underlying genetic condition, malformations that may accompany the hernia may occur. It is possible to encounter malformations of the heart, kidney, brain and gastrointestinal organs. Cardiac pathologies in particular are the most common accompanying malformations (table 2) [6]. For this reason, a detailed fetal echo should be done in cases with diaphragmatic hernia.

Syndromes that can be seen in the presence of congenital diaphragmatic hernia			
Trisomy 18	Trisomy 13	Tetrasomy 12p (pallister-killian syndrome)	Fyrns syndrome
Apert syndrome	CHARGE syndrome	Coffin-siris syndrome	Perlman syndrome
Goltz syndrome	Perlman syndrome	Swyer syndrome	Cornelia de lange syndrome
Goldenhar sequence	Beckwith-wideman syndrome	Simpson-golabi-behmen syndrome	Donnai-barrow syndrome
Mattew-wood syndrome	Jarcho-levin syndrome	Fraser syndrome	Pierre-robin syndrome

Table-1: Syndromes that may accompany diaphragmatic hernia

The majority of congenital diaphragmatic hernia cases develop sporadically [8]. However, in some cases, familial transmission can be observed [9]. The underlying cause in sporadic cases is not clearly known. Vitamin A deficiency or the use of drugs such as allopurinol-lithium can be considered among other rare causes in etiology.

	Defect type	Frequency
Cardiac malformations	Ventricular septal defect	6%
	Atrial septal defect	3%
	Aortic coarctation, Hypoplastic left heart syndrome	2%
	Dextrocardia, Tetralogy of Fallot, single ventricle, tricuspid atresia, pulmonary stenosis	1%
Gastrointestinal malformations	Malrotation	4%
	Imperforate anus	3%
	Gallbladder agenesis, accessory spleen	1%
Urogenital anomalies	Renal agenesis	3%
	Cystic kidney, testicular agnesis, bicornuate uterus	1%
Musculoskeletal anomalies	Absence of limbs	5%
	Club foot	4%
	Omphalocele	3%
	Vertebral anomalies, arthrogryposis, sternal defect	2%
	Abdominal wall defect, rib anomalies, hip dislocation, ectopia cordia	1%
Respiratory system anomalies	Pulmonary secretion, tracheoesophageal fistula	1%
Central nervous system anomalies	Neural tube defect, hydrocephalus	3%
	Ocular hypoplasia	1%
Craniofacial defect	Cleft lip / palate	2%

Table 2: Defects associated with congenital diaphragmatic hernia

Diagnosis:

The first diagnosis is made by ultrasound. Although it is usually detected in a detailed ultrasound examination performed around the 20th week, if the defect is of serious size, there is a chance that it can be detected in the first trimester or early second trimester. If there are other accompanying malformations, the chance of detecting a diaphragmatic hernia will also increase. Usually the first sign is mediastinal shift and anechoic gastric pocket in the thoracic cavity. If the liver is present in the herniated area, it will identify itself as a hypoechoic mass next to the heart. Usually the left lobe of the liver is herniated. Diagnosis becomes more difficult in diaphragmatic hernias occurring on the right side. Because, gastric herniation does not occur in hernias from the right side. Therefore, the gastric pocket, which has a high diagnostic effect, cannot be observed in the intrathoracic region. The right-herniated liver may be difficult to distinguish as it resembles lung in echogenicity. The most effective and easiest method for determining liver herniation is to monitor the liver vessels in the intrasthoracic region with Doppler ultrasound. Especially in the third trimester, polyhydroamnios findings may occur due to impaired fetal swallowing. Serious mediastinal shift may

occur in hernias due to large defects and hydrops fetalis may develop in the early weeks of pregnancy.

While performing ultrasonographic examination, the diaphragm should be scanned with all its lines and its intact structure should be documented. Coronal plan evaluations may not detect defects, especially in the posterior area. For this reason, ultrasonographic examination should be done in sagittal section.

Although magnetic resonance (MR) imaging has more advantages than ultrasound, it is always possible to capture the first findings on ultrasound. Total lung volume measurement (important for prognosis) can be measured more precisely with MRI imaging. In addition, liver herniation and other organ herniations can be selected more clearly. It is less likely to be affected by conditions that impair the image quality in ultrasound, such as maternal obesity and oligohydramnios.

Prognosis:

The prognosis may vary depending on many factors. If there is an accompanying chromosomal defect, the prognosis usually depends on the type of chromosomal defect and the type of accompanying organ malformation. In particular, the type of cardiac defect provides a significant determinant of prognosis [10]. Some studies have shown that the prognosis for right hernias is worse [11].

If diaphragmatic hernia is isolated, the most important factor in prognosis is the amount of lung tissue left after compression. Many measurement methods have been defined to predict the remaining amount of lung tissue. The most known of these measurement methods is the 'Lung to Head Ratio' (LHR) ratio. In this measurement, the ratio of the lung tissue area on the opposite side of the herniated side to the head circumference is taken. The lung area can be found by measuring the circumference of the lung (tracing method) or it can be found by multiplying the two longest diameters of the lung. Both measurements are measured in millimeters and their ratios are calculated. The section where the measurement was taken should be the section where the 4-chamber image of the heart was taken. If the LHR is less than 1, it is possible to say that the prognosis is poor and it will require extra corporal membrane oxygenation (ECMO) in the postpartum period. If there is a ratio of more than 1.4, it is estimated that the prognosis may be good. It is known that fetal lung development is 4 times faster than fetal brain development especially in the early 2nd trimester. Inconsistencies may be observed between gestational age and LHR rates due to the difference in growth rate. Based on this situation, it was predicted that the LHR ratio may give inconsistent values about postpartum prognosis depending on gestational age [12]. For this reason, the 'observerd / expected LHR' (o / e LHR) ratio is becoming more up-to-date today as a measurement method independent of gestational age. After the lung measurement is taken ultrasonographically, the o / e LHR ratio is calculated by entering data into automatic calculators. It can be said that the prognosis is poor at rates below about 45% (very poor prognosis for values less than 25%). Values higher than 45% are associated with high survival rates. In the guideline published by 'The Canadian Congenital Diaphragmatic Hernia Collaborative' in 2019, poor prognosis criteria are defined differently. If the hernia is on the left side, it is emphasized that the o / e LHR ratio should be 25% in order to be able to say that it is a bad prognosis. However, they emphasized that in order to be able to say that right-sided hernias have a poor prognosis, higher limit values are required (45%) [13].

Another measurement method used to predict prognosis is "Quantitative lung index" (QLI). It is the mathematical equation that describes the enlargement of the right lung [14]. Since it is defined only for the right lung, it can only be used in cases with left hernias. Between the 16th and 32nd weeks, the QLI is about 1. If this value is calculated as less than 0.6, postnatal poor prognosis is expected.

A modified McGoon index has been defined to predict whether pulmonary hypertension will develop in the postpartum period [15]. The purpose of this calculation is to calculate the risk of pulmonary hypertension in the postpartum period [16]. Right and left pulmonary artery diameters are measured and collected. This total constitutes the numerator part of the division. The diameter of the aorta is determined in the measurement made from the level of the diaphragm and this constitutes the denominator part of the division process. If the rate obtained is <1, it can be said that severe hypertension may develop in the neonatal period (figure 1).

$$\frac{RPA + LPA}{AoR}$$

Figure 1: modifiye McGoon indeksi (RPA:sağ pulmoner arter, LPA: sol pulmoner arter, AoR: Aorta)

Hernia of the liver tissue is another poor prognostic factor [17]. In addition, the defect on the right side, bilateral or large hernia, and comorbid polyhydramios are other poor prognostic factors (table 3).

Poor prognostic factors in congenital diaphragmatic hernia
Accompanying malformations
Accompanying chromosomal abnormalities
o / e LHD <25%
Estimated lung volume <20 mL
Right-sided hernia
Left ventricular hypoplasia of the heart
polyhydramnios
Liver herniation
Wide defect

Table 3: Poor prognostic factors in congenital diaphragmatic hernias

Fetal Endoscopic Tracheal Occlusion:

In the last two decades, in parallel with the developments in ultrasound and MRI, it has become more possible to determine the fetal prognosis. Fetal treatment options have begun to be investigated in pregnant women with diaphragmatic hernia with poor prognosis. First, Harrison et al. performed tracheal obstruction experiments on animal models. Since then, tracheal occlusion studies have come a long way [18].

The purpose of tracheal occlusion is to prevent pulmonary fluids from draining from the trachea into the amniotic fluid and to accumulate in the lung. These accumulated fluids cause lung volume expansion. Surfactant production increases due to volume expansion and pulmonary hypertension level decreases. It is not clear yet for which patients tracheal occlusion will be an option. In 2010, the European Fetal Endoscopic Tracheal Occlusion Working Group determined the conditions under which the patient could be a candidate for tracheal occlusion and created a web address (Tracheal Occlusion to Accelerate Lung Growth) (totaltrial) (table 4) [19].

Inclusion criteria	18 years and above (who can give consent for the procedure)
	Single pregnancy
	Isolated diaphragmatic hernia and normal chromosomal structure
	Left-sided diaphragmatic
	Week of gestation <29 weeks + 5 days
	Poor lung area (o / e LHR <25%)
	Having the appropriate hospital for the procedure
Exclusion criteria	Mother contraindicated for fetal surgery (maternal severe comorbidities)
	Unrelated conditions (fibroids, unsuitable fetal position)
	Prterm action
	Short cx (<15mm)
	Placenta previa (in terms of being preterm labor)
	Age <18
	Right-sided diaphragmatic hernia
	Presence of other malformations accompanied by hernia
	Abnormal chromosomal structure

Table 4: Fetal tracheal occlusion indications and contraindications prepared by the European Fetal Endoscopic Tracheal Occlusion Working Group

The procedure is applied when the gestational age is between 27 weeks + 0 days and 29 weeks + 6 days in patients with congenital diaphragmatic hernia (in cases with very poor prognosis, the procedure can be performed earlier, but the possibility of complications increases). Local anesthesia (spinal / epidural) is sufficient in most cases [20]. The localization of the placenta and the fetal position should be determined with ultrasound. An external version may be required to bring the fetal mouth closer to the anterior. After the fetal position is observed to be suitable, fentanyl and atropine are administered into intraamniotic fluid to restrict fetal movement and prevent fetal bradycardia. The European Fetal Endoscopic Tracheal Occlusion Working Group recommends inserting a 3.3 mm diameter trocar into the abdomen and uterus. A 3.3mm diameter trocar is first entered into the uterus, then the endoscope is passed through the fetal mouth to try to pass into the trachea. After the vocal cords are seen, they are passed through and the endoscope is pushed up to the carina. After reaching the carina level, the balloon is started to be inflated, the endoscope is withdrawn and the balloon is left between the carina and vocal cords. The balloon is inflated with 0.6 mL of isotinic liquid [20].

The diameter of the balloon is 7mm and its length is around 20mm. Afterwards, the endoscope is withdrawn and removed from the uterus and abdomen.

The general idea is to keep the bubble inside until the 34th week [21]. The balloon can be removed with two methods within 34 weeks. In the first method, it is entered with a trocar similar to its insertion. After the balloon is seen, it is punctured with the needle passed near the endoscope and the balloon is removed. The second method is to enter with an ultrasound-guided amionsynthesis needle, pass through the neck and blow the balloon. It is expected that the ruptured balloon spontaneously reaches the amniotic fluid. Apart from these two methods, another method of removal has been defined. The balloon is not removed until delivery, and before the placenta is separated during delivery, the fetal pharynx and larynx are made visible and the balloon is deflated and removed [22]. It is a less accepted method than the previous two methods.

Results of Fetal Endoscopic Tracheal Occlusion Procedure:

There are no common studies in the literature regarding the tracheal occlusion procedure. In 2016, Ali et al. compared 43 tracheal occluded diaphragmatic hernias with 35 non-occluded diaphragmatic hernias [23]. They found that the occlusion group required longer postpartum ventilation. In addition, they observed that there was a higher number of preterm labor in the occluded group. Belford et al. Examined the results of 11 occlusion cases in 2017 [24]. They observed preterm premature rupture of membrane in 27% of the cases who underwent occlusion. They found that survival rates increased in a statistically significant way. Al-Maary et al. Analyzed 211 cases in the literature in a meta-analysis published in 2016 and found that there was an increase in postpartum survival in patients who underwent occlusion [25]. In 2019, Style et al. retrospectively reviewed the results of 257 patients to investigate the effect of tracheal occlusion on pulmonary hypertension [26]. They found that the rate of pulmonary hypertension after 1 year was lower in babies who had tracheal occlusion in the prenatal period. Although it is thought that the tracheal occlusion procedure can only be applied in left-sided hernias, Veeken et al., In their article published in 2018, stated that this procedure can also be used safely in right-sided hernias [27]. Similarly, although there is no indication, there are researchers who have tried tracheal occlusion in non-isolated diffragmatic hernias. Seravalli et al. In 2017, they applied tracheal occlusion to two cases with non-isolated diaphragmatic hernia and stated that they achieved successful results [28].

Conclusion:

Fetal endoscopic tracheal occlusion is a promising treatment method for diaphragmatic hernia in the future. Currently, there is no prenatal treatment for diaphragmatic hernia. With the available data, the only prenatal treatment that can be done for now seems like fetal endoscopic tracheal occlusion. Planning occlusion therapy, especially in patients with poor prognostic factors, increases the survival rate of the newborn. However, this treatment seems to need more extensive research in order to be put into routine practice. For now it should still be considered as an experimental treatment.

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