OUTCOMES OF CONGENITAL CYSTIC LUNG MALFORMATIONS IN CHILDREN AND THEIR MANAGEMENT ACCORDING TO CLINICAL PROGRESSION

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The aim of the investigation was to analyze the outcomes of congenital cystic lung malformations in children in accordance with clinical manifestations in pre- and postnatal period, and justify the management of patients.

Materials and Methods. We analyzed retrospectively 45 cases of congenital cystic lung malformations treated over a period from 2005 to 2012 in two main children hospitals in Nizhny Novgorod.

Results. Congenital cystic adenomatoid malformation (CCAM) is the most common congenital cystic lesion of the lung (60%). Nearly half children with this pathology have no respiratory signs in neonatal period, and in 22.2% cases there are no manifestations in early childhood either. Three cases were found to have spontaneous regression of CCAM. Cystic adenomatoid malformation and solitary congenital cysts have the most favorable prognosis if prenatal lung lesions are early detected and there are no associated congenital malformations. Only 13% children (28.8%) required surgical resection of cystic lung malformations. The survival rate of children with cystic lung malformations after surgery was 92.3%.

Conclusion. Favorable outcomes of pregnancies with cystic lung diseases constituted the majority (86.7%) of cases. Operative treatment is indicated if there are respiratory failure signs or recurrent respiratory infections.

Key words: cystic lung lesion; congenital cystic adenomatoid malformation; cystic malformation; congenital lobar emphysema; bronchopulmonary sequestration; congenital pulmonary cyst.

The management of congenital lung malformations (CLM) up to the present remains one of the urgent medical problems. Cystic lung malformations are the most common abnormalities of lung. Classical cystic CLM include congenital cystic adenomatoid malformation (CCAM), congenital lobar emphysema (CLE), bronchopulmonary sequestration (BPS) and congenital pulmonary cysts. CLM incidence is about 1 per 10 000–25 000 births [1]. Such malformations are characterized as potentially life-threatening lung lesions in children. According to some authors, a congenital lung malformation is one of the main causes of perinatal death rate and neonatal incidence: antenatal mortality of fetuses with congenital lung malformations accounts for 6.6%, neonatal mortality in congenital lung malformations — 13.3% [2].

Recently, CLM are detected in antenatal period more frequently by ultrasound that enables to solve the problem of surveillance of such patients in due course [3]. Screening of congenital cystic lung abnormalities using ultrasound can be used since the 20th gestation week. Increasingly greater number of lung malformations is detected antenatally. Currently, the management of such patients is still controversial [4].

Despite a significant progress in qualified medical care delivery for infants, the treatment results of CLM are not always reassuring. This fact is explained by the absence of an orderly system of prenatal diagnosis, effective treatment and prevention. In many cases there remains an open question of an optimal surgery time in CLM, as there is no concurrent view on many intensive care aspects, anesthetic techniques and developmental care of newborns with this pathology [5].

Congenital bronchopulmonary defects are oftimes the basis for secondary infection resulting in chronic inflammatory pulmonary diseases [6]. According to some authors [5, 7, 8], congenital malformation prevalence in patients with chronic lung diseases is in the range from 1.4–10 to 20–60% that can be explained by the fuzziness of both clinicoradiological and pathomorphological diagnostic criteria of some congenital defects, particularly those complicated by chronic inflammation and fibrous changes.

The aim of the investigation was to analyze the outcomes of congenital cystic lung malformations in children in accordance with clinical manifestations in pre- and postnatal period, and justify the management of patients.

Materials and Methods. We carried out a retrospective study of 45 cases of cystic lung malformations in children

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over the period from 2005 to 2012 to characterize the course and determine the management of congenital cystic lung malformation. Depending on the time of establishing a diagnosis there were performed prenatal diagnosis including routine ultrasonic examination, genetic counseling, and postnatal diagnosis including chest radiography of children, chest multispiral computed tomography, diagnostic tracheobronchoscopy.

We analyzed fetal ultrasonic findings and dynamics of ultrasonic data in an antenatal period, accuracy of malformation diagnosis, age at the moment of diagnosis, clinical signs after birth, chest radiograph and multispiral computed tomography findings, the results of surgery and pathomorphological study of removed tissue, long-term clinical data of patients and total survival rate estimate of children with CLM. There was assessed the structure of cystic CLM, the prevalence of concomitant congenital abnormalities. Perinatal outcomes in fetuses and children with CLM were estimated by the ratio of dead born, dead, and living children; neonatal and postneonatal infant mortality being studied.

The retrospective study was approved by the Ethic Committee of Nizhny Novgorod State Medical Academy, and complies with the declaration of Helsinki (adopted in June, 1964 (Helsinki, Finland) and revised in October, 2000 (Edinburg, Scotland)). All patients gave their written informed consent to have their data analyzed.

The study was based on the following records: a child`s record, a case history, an ultrasonic fetal assessment protocol, and in case of postnatal death — an autopsy study protocol of nonsurviving fetuses and infants. Surgical treatment of the defects was performed in Nizhny Novgorod Regional Children Clinical Hospital and Nizhny Novgorod Children City Clinical Hospital No.1. Fetal sonography was carried put in Regional Diagnostic Centre (Nizhny Novgorod) on Toshiba Aplio XG and VOLUSION E-8 (Japan) using transabdominal and transvaginal ultrasound.

Analysis data were statistically processed according to the principles of evidentiary medicine using computer-assisted assay and integrated software package Statistica 6.0, Windows XP.

Results. Of 45 cases of cystic lung malformations 14 (31.1%) belonged to girls and 31 (69.9%) — to boys. Mean age of pregnant women was 26.07±4.80 years. Mean age of fetuses and newborns at the moment of establishing diagnosis was 43.3±32.6 weeks of postconception age (from 20 gestation weeks to 2 years 10 months after birth) (Fig. 1).

In 19 cases (42.2%) the detected by prenatal ultrasound in women with 20-week gestation age. Mean age of defect detection prenatally was 22.80±3.35 weeks. 8 children (17.8%) were diagnosed during antenatal period. In 12 cases (26.6%) the diagnosis was made as early as in young age, in 6 cases (13.3%) — the diagnosis was made post mortem, after infant`s death.

Among the malformations detected there were 27 cases (60%) of CCAM, 7 cases (15.6%) — CLE, 8 cases (17.8%) — pulmonary cyst, 1 case — BPS, and 2 cases — CLE combined with CCAM.

Perinatal outcomes of fetuses and children with congenital cystic lung malformations are as follows (Fig. 2): in three cases there was premature delivery with a fetal death. The rest 42 pregnancies (93.3%) proceeded to live-birth delivery, among them there were 32 cases (83.3%) of delivery at term. Four neonates died during a neonatal period: two of them died at the age of 8 days, 1 — at the age of one day, and 1 late neonatal death was recorded at the age of 15 days. One infant aged 3.5 months died in a postnatal period. Among 7 unfavorable outcomes of cystic lung malformations, only once the diagnosis was made at the age of 3 months, in other cases the defect was newly diagnosed post mortem, after the death of a fetus or an infant. There were none death cases of patients with CLM diagnosed prenatally. Four patients with unfavorable outcomes of cystic lung malformations were recorded to have multiple congenital abnormalities, among them there were two cases of CLM combined with congenital diaphragmatic hernia, and one case — with congenital defect of central nervous system (spina bifida), heart and Potter syndrome. In all cases severe accompanying defects were detected by antenatal ultrasound, all patients were

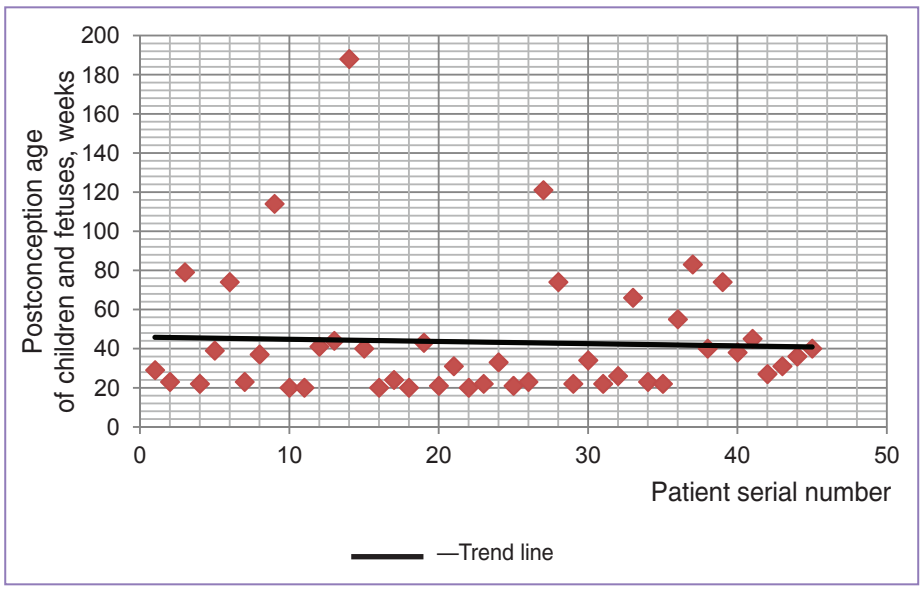

Fig. 1. Fetal age and age of children at the time of diagnosis

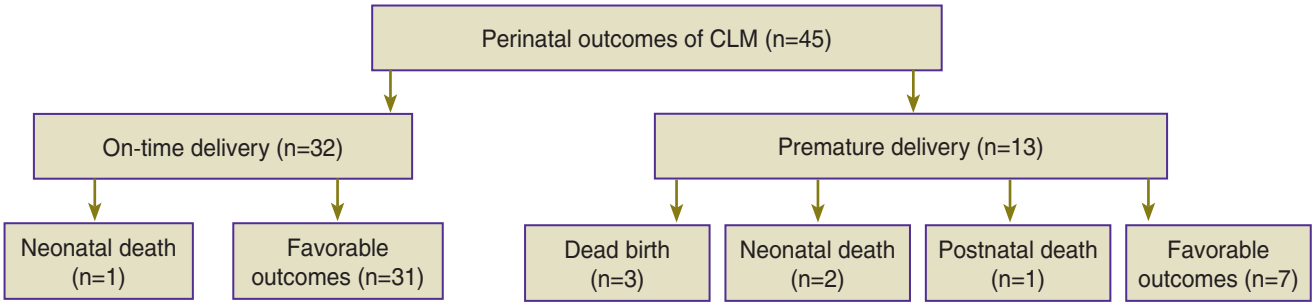

Fig. 2. Perinatal outcomes in fetuses and children with congenital cystic lung malformations

Clinical characteristic and outcomes of cystic lung malformations under study

Characteristics	CCAM	CLE	BPS	Congenital cyst	CCAM+ CLE	Total
Number of cases	27	7	1	8	2	45
Sex (male/female)	20/7	4/3	0/1	6/2	1/1	31/14
CLM diagnostic time (prenatal/postnatal/postmortem)	14/8/5	1/6/0	1/0/0	6/1/1	1/1/0	23/16/6
Symptomatic/asymptomatic abnormalities	18/6	7/0	1/0	6/2	2/0	34/8
Clinical manifestations (neonatal/postneonatal period)	12/5	6/1	1/0	1/5	2/0	23/11
Surgical/conservative treatment	2/25	5/2	1/0	3/5	2/0	13/32
Postoperative lethal outcome	0	1	0	0	0	1
Presence/absence of associated congenital malformations	8/19	3/4	0/1	5/3	0/2	16/29
Outcomes (dead born/non-surviving/living children)	3/2/22	0/1/6	0/0/1	0/1/7	0/0/2	3/4/38

found to have various confounding factors: hydramnion, mediastinal shift, placenta pathology. Three children had isolated congenital malformations of respiratory system including one case with the combination of CLE and tracheal bronchus. 38 children (84.4%) with CLM had favorable perinatal outcomes.

23 of 42 live-birth infants (54.8%) were found to have clinical manifestations of the malformation in a neonatal period, among them respiratory distress-syndrome — in 11 patients, respiratory infection/pneumonia — in 7, and dispnoea — in 6. In 11 children the defect first presented clinically at the age from 1 month to 3 years including 80% cases of recurrent broncho-obstructive syndrome or respiratory infection/pneumonia. However, 8 children were clinically asymptomatic within the young age period.

22 children of 45 (48.9%) had mediastinal shift to a healthy side, in 12 (26.7%) congenital lung malformations were associated with other congenital abnormalities, among them 4 patients were detected to have congenital cardiovascular defect, 5 — congenital malformations of trachea and bronchi (tracheomalacia, bronchomalacia, tracheal bronchus, tracheal or bronchial stenosis), 2 — congenital malformations of musculoskeletal system (congenital diaphragmal hernia), and 1 — congenital cardiovascular malformations (spina bifida).

13 children (28.8%) underwent surgical correction of the defect (CCAM — 2, CLE — 5, congenital cyst — 3, BPS — 1, CLE with CCAM — 2). The age of the operated children varied from 7 days to 6 years. Lung tissue reduction was performed within the limits of a cyst, a segment and an affected lobe. In 1 case of CLE complete surgical defect correction failed due to the deterioration of a patient`s state resulted in a lethal outcome. 4 patients had postoperative complications (pneumothorax, pleurisy). Survival rate of children with cystic lung malformations after surgery was 92.3%.

In 3 cases the diagnosis was changed postoperatively according to pathomorphological findings: CCAM was detected instead of a congenital cyst in 1 case, CLE with cystic transformation of pulmonary tissue instead of CCAM was found in 2 children.

The table represents the characteristics of each group of cystic lung malformations.

Congenital cystic adenomatoid lung disease (n=27). Prenatally there were revealed 14 cases of 27 CCAM (52%), among them three children appeared to have cyst regression till complete resolution by the end of the third trimester. 8 children were diagnosed after birth, in 4 among them — in a neonatal period, in 3 — during the first year. And in one child the defect was detected at

the age of 1.5 years. In 5 cases the diagnosis was first made post mortem, among them there were 3 cases of type 3 CCAM according to Stocker classification [9].

In 13 live-birth infants (54.2%) the malformation made its first appearance in a neonatal period by respiratory symptoms, respiratory distress-syndrome constituting the half of symptoms.

11 children (45.8%) had no clinical manifestations at birth including 5 children who had respiratory infection (bronchitis, pneumonia) during the first year. 6 cases of 11 remained asymptomatic during the young age.

12 patients (44.4%) had a right-sided process, 7 — left-sided, 4 — a bilateral defect. 11 children (40.7%) were found to have mediastinal shift to the health side, in 25 children (92.5%) 3 and more cysts could be found in the lung. In 18 patients (66.7%) cysts were inside one lobe. Type 1 malformation was detected in 10 cases, type 2 — in 9, and type 3 — in 8 patients.

Survival rate of children with CCAM was 81.5% (3 cases of dead birth, 2 — an early neonatal death). 100% of dead children and fetuses were found to have multiple congenital abnormalities.

Emergency surgical cyst excision was performed only once, and one child had a planned surgery at the age of 3 years, the rest children were recommended a follow-up radiographic evaluations.

Congenital lobar emphysema (n=7). Among children with CLE only one diagnosis was made prenatally by ultrasonic fetal assessment. The rest cases were diagnosed after birth, in a neonatal period. In 6 children the malformation made its debut in an early neonatal period by respiratory failure symptoms, in 4 — the defect was found in the upper lobe of the left lung, and 5 children had mediastinal shift.

5 patients required surgery (4 — lobectomy, 1 — biopsy). The age of operated patients varied from 1 week to 6 years, the complication being revealed in 2 cases: a child died of cardiopulmonary decompensation and partially pressure pneumothorax.

Congenital pulmonary cysts (n=8). In two cases a cyst was imaged on prenatal screening ultrasonic examination at 22-week gestation. None malformations were detected in a neonatal period. In 5 children the diagnosis was made in an early age period (from 3.5 months to 2 years 10 months). In one case a cyst was found post mortem, the infant had multiple congenital malformations (congenital diaphragmal hernia, intestinal malrotation, dorsal common mesentery and pulmonary hypoplasia) and died at the age of 15 days. The infant had clinical manifestations of the malformation immediately after birth, and was operated on at the age of 7 days for congenital diaphragmal hernia, however, at the age of 15 days the boy died. In 6 cases the defect had no clinical manifestations till the age from 5 months and to 2 years 10 months after birth. Associated congenital abnormalities were found in 5 patients, among them three children had congenital bronchopulmonary malformations (tracheomalacia, bronchomalacia, pulmonary hypoplasia, lobar emphysema). In 6 patients a cyst was located in the right lung, including 5 patients with a cyst in the lower lobe. Medistinal shift was detected in 4 cases, the cyst size varying from 4.5 to 7.5 cm in diameter, in two children giant cysts occupied the half of the chest prolapsing towards the opposite side. 4 patients underwent surgical cyst excision. The age of the operated children varied from 17 days to 2 years 10 months. Postoperative complication (pneumothorax) was found in one case.

Bronchopulmonary sequestration (n=1). In our survey there was only one case of BPS. The defect was first suspected in a 24-week fetus. He was born at term, though since birth had respiratory failure symptoms. His condition was estimated as severe. On first day after birth the newborn was found to have also pneumonia, pneumothorax on the opposite side, mediastinal shift. At the age of 1 month he was operated on. The postoperative period was uneventful.

Congenital lobar emphysema combined with CCAM (n=2). In two cases CLE with cystic adenomatoid pulmonary tissue alteration was revealed pathomorphologically. In one child the malformation was first suspected as CCAM prenatally, at the second screening ultrasound investigation, in another the defect was not detected prenatally, though the pregnancy had resulted from in vitro fertilization, and the woman was at bed rest in hospital during all gestation period. In both cases the defect was clinically detected in a neonatal period and the children were immediately operated on in critical situations. In both cases histological examination of excised pulmonary tissue revealed the combination of CCAM and CLE. The literature describes the combination of these defects, as well as the combination of CCAM and BPS [10]. These reported combinations of CLM raise the question of their reclassification.

Discussion. Due to the advances in prenatal ultrasonic diagnosis, the prevalence of cystic lung malformations is growing, CCAM being the most common among them (60% cases). In 42.2% cases CLM are detected by routine fetal sonography at the beginning of the second trimester. Successive ultrasound investigation in a gestational period enables to monitor the changes and evolution of most malformations.

The literature [11–13] describes the cases of intrauterine antenatal CCAM regression; however, there are a few reports on cyst regression in a postnatal period. In our study we revealed intrauterine malformation regression in three cases, as well as spontaneous postnatal regression in one patient at the age of 1.5 months. Theoretically, the malformations can disappear, but their continuous regression after birth should not be ruled out, since the lungs keep developing till the age of 3–7 years [11, 14].

Our data on high percentage of an asymptomatic course are supported by the cases reported in literature [15].

In our study 45.8% of children with CCAM had no respiratory symptoms at birth, and 22.2% presented no symptoms till the age of 3 years. This fact suggests that expectant management with dynamic monitoring of the malformation in such cases is the most reasonable. A surgery in newborns with asymptomatic CCAM is to be delayed till 3-year age — it will make it possible to reduce the size of cysts and by that facilitate the surgery. Moreover, there is still the probability of complete remission of the malformation [16]. Therefore, all patients should undergo multidetector computed tomography aimed at more detailed imaging of the lungs. However, we cannot rule out completely the histological changes.

Respiratory failure is the most common clinical manifestation in newborns with CCAM, while in children of early age lung malformations are frequently presented by recurrent respiratory infections and/or obstructive syndrome. According to our data, bronchites appear in 69% cases in children with cystic lung malformations in early childhood. Most CCAM cases are — unilobar, only a few children have several lobes involved, and more rarely — bilateral involvement. Only 4 patients had multilobar involvement, all of them having bilateral lung disease.

In contrast to CCAM, congenital lobar emphysema in most cases (85.7%) presents by respiratory failure symptoms since birth, therefore, 57.1% of children with CLE were operated on during the first year of life, and it is more frequently than in children with CCAM (3.7%).

Solitary congenital lung cysts are less frequently accompanied by any respiratory symptoms in a neonatal period. In our study only in two cases we stated clinical presentations of congenital cysts; however, these children also had accompanying congenital defects (diaphragmal hernia, lobar emphysema). It should be noted that congenital lung cysts are most frequently accompanied by other congenital bronchopulmonary malformations (60% cases).

Currently, there are still different views on the management of children with CLM. In literature there are reports about intrauterine treatment of cystic changes using laser ablation techniques [17, 18]. However, this modality is not always appropriate, since it is important to trace the changes of cyst sizes. Postnatal surgical treatment of cystic lung malformations aims at improvement and stabilization of clinical state of a child and prevention of early complications, such as pneumothorax, progressive respiratory failure, infections and malignant transformation. Follow-up is significant for those patients who have rapid arresting of respiratory insufficiency immediately after birth, with no concurrent abnormalities, as it can help to escape an unnecessary surgery. However, an immediate operation can be useful for children with clinical debut at an older age, since spontaneous malformation regression at this age occurs much more rarely [11].

Conclusion. Favorable outcomes of pregnancies with cystic lung malformations in fetuses and children constitute an absolute majority (86.7%) of cases. Unfavorable outcomes are primarily associated with multiple congenital abnormalities, due to which it is reasonable to have such pregnancies terminated at early stages.

Cystic adenomatoid lung disease is the most common (60%) among congenital cystic lung malformations. A half of children (45.8%) with this pathology have no respiratory signs in a neonatal period, and in 22.2% of cases no symptoms appear in an early age period.

Cystic adenomatoid lung malformations and solitary congenital cysts have more favorable prognosis on condition of early detection of malformations during a prenatal period and the absence of concurrent congenital defects.

Prenatal diagnostics of congenital lung malformations does not mean the surgery is required. Operative treatment is indicated only when there is a marked presentation of respiratory failure or recurrent respiratory infections.

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References

1. Lakhoo K., Mngongo C. Congenital cystic lung lesion. In: E.A. Ameh, S.W. Bickler, K. Lakhoo, et al. *Paediatric surgery: a comprehensive text for Africa*. Seattle, WA, USA: GLOBAL HELP Organization; 2011; p. 287–291.

2. Kokhno N.I. *Vrozhdennye zabolevaniya legkikh ploda (techenie beremennosti, diagnostika i iskhody).* Avtoref. dis. ... kand. med. nauk [Congenital lung diseases (gestation course, diagnosis and outcomes). Abstract of Dissertation for the degree of Candidate of medical science]. Moscow; 2005; 195 p.

3. Kulakov V.I., Isakov Yu.F., Kucherov Yu.I., Baybarina E.N. Prenatal diagnosis and management of congenital malformations in recent times. *Rossiyskiy vestnik perinatologii i pediatrii* 2006; 6: 63–65.

4. Laberge J.M., Flageole H., Pugash D., et al. Outcome of the prenatally diagnosed congenital cystic adenomatoid lung malformation: a Canadian experience. *Fetal Diagn Ther* 2001; 16: 178–186, http://dx.doi.org/10.1159/000053905.

5. Korolev B.A., Shakhov B.E., Pavlunin A.V. *Anomalii i poroki razvitiya legkikh* [Pulmonary anomalies and malformations]. Nizhny Novgorod: Izd-vo NizhGMA; 2000; 302 p.

6. Kaganov S.Yu., Rozinova N.N. Mesto vrozhdennoy i nasledstvennoy patologii v pul'monologii detskogo vozrasta. V kn.: *Vrozhdennye i nasledstvennye zabolevaniya legkikh u detey* [The position of congenital and hereditary defects in pediatric pulmonology. In: Congenital and hereditary lung diseases in children]. Pod red. Yu.E. Vel'tishchev, S.Yu. Kaganov, V. Tal' [Yu.E. Vel'tishchev, S.Yu. Kaganov, V. Tal' (editirs)]. Moscow: Meditsina, 1986; p. 9–22.

7. Cherenkov Yu.V., Nechaev V.N. Diagnosis, prevention and correction of congenital malformations. *Saratovskiy nauchno-meditsinskiy zhurnal* 2009; 5(3): 379–383.

8. Yatsyk G.V., Davydova I.V., Tsygina E.N., Kustova O.V., Basargina M.A. Diagnostics of congenital bronchopulmonary diseases in children after neonatal ALV. *Praktika pediatra* 2008; Marsh: 62–65.

9. Biyyam D.R., Chapman T., et al. Congenital lung abnormalities embryologic features, prenatal diagnosis, and postnatal radiologic-pathologic correlation. *RadioGraphics* 2010; 30(6): 1721–1737, http://dx.doi.org/10.1148/rg.306105508.

10. Newman B. Congenital bronchopulmonary foregut malformations: concepts and controversies. *Pediatr Radiol* 2006; 36(8): 773–791, http://dx.doi.org/10.1007/s00247-006-0115-4.

11. Sui-Ling Liao, Shen-Hao Lai, Chuen Hsueh, Kin-Sun Wong. Comparing late-onset and neonatally-diagnosed congenital cystic adenomatoid malformation of the lung. *Chang Gung Med J* 2010; 33(1): 36.

12. Crombleholme T.M., Coleman B., Hedrick H., Leichty K., Howel L., Flake A.W., Johnson M., Adzick N.S. Cystic adenomatoid malformation volume ratio predicts outcome in prenatally diagnosed cystic adenomatoid malformation of the lung. *J Pediatr Surg* 2002; 37(7): 331–338, http://dx.doi.org/10.1053/jpsu.2002.30832.

13. Butterworth S.A., Blair G.K. Postnatal spontaneous resolution of congenital cystic adenomatoid malformations. *J Pediatr Surg* 2005; 40(5): 832–834, http://dx.doi.org/10.1016/j.jpedsurg.2005.01.051.

14. Guttentag S., Ballard P.L. Lung development: embryology, growth, maturation, and developmental biology. In: W. Taeusch, R.A. Ballard, C.A. Gleason, eds. *Avery's Disease of the Newborn.* Philadelphia: Elsevier Saunders, Inc.; 2005; p. 601–608.

15. Sood M., Sharma S. Congenital cystic adenomatoid malformation lung — a case report. *Curr Pediatr Res* 2011; 15(1): 61–63.

16. Marshall K.W., Blane C.E., Teitelbaum D.H., Leeuwen K.V. Congenital cystic adenomatoid malformation: impact of prenatal diagnosis and changing strategies in the treatment of the asymptomatic patient. *AJR Am J Roentgenol* 2000; 175: 1551–1554.

17. Cavoretto P., Molina F., Poggi S., Davenport M., Nicolaides K.H. Prenatal diagnosis and outcome of echogenic fetal lung lesions. *Ultrasound Obstet Gynecol* 2008; 32: 769–783, http://dx.doi.org/10.1002/uog.6218.

18. Nadeem M., Elnazir B., Greally P. Congenital pulmonary malformation in children. *Scientifica* 2012, 2012: 7, http://dx.doi.org/10.6064/2012/209896.